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Annals of Surgery

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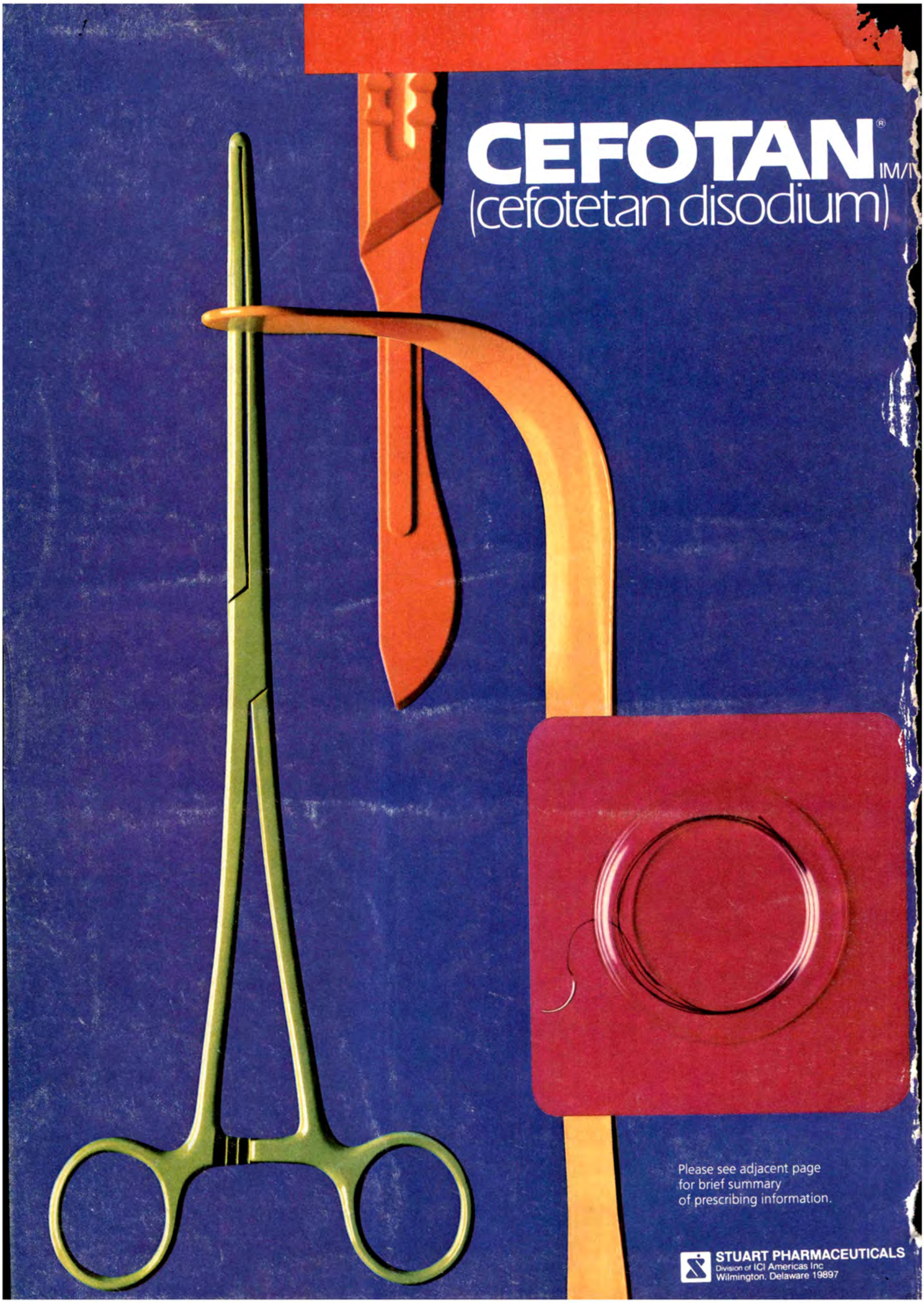

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(cefotetan disodium)

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P, 24, 798

The cost-effective replacement for cefoxitin

For Intravenous or Intramuscular Use

BRIEF SUMMARY

INDICATIONS AND USAGE
TREATMENT: CEFOTAN® (cefotetan disodium) is indicated for the therapeutic treatment of the following infections when caused by susceptible strains of the designated organisms:

Urinary tract infections caused by *E coli*, *Klebsiella* species (including *K pneumoniae*), *Proteus mirabilis* and *Proteus* sp (which may include the organisms now called *Proteus vulgaris*, *Providencia rettgeri*, and *Morganella morganii*).

Lower respiratory tract infections caused by *Streptococcus pneumoniae* (formerly *D pneumoniae*), *Staphylococcus aureus* (penicillinase- and nonpenicillinase-producing strains), *Haemophilus influenzae* (including ampicillin-resistant strains), *Klebsiella* species (including *K pneumoniae*), and *E coli*.

Skin and skin structure infections caused by *Staphylococcus aureus* (penicillinase- and nonpenicillinase-producing strains), *Staphylococcus epidermidis*,* *Streptococcus pyogenes* and *Streptococcus* species (excluding enterococci), and *E coli*.

Gynecologic infections caused by *Staphylococcus aureus*† (including penicillinase- and nonpenicillinase-producing strains), *Staphylococcus epidermidis*,* *Streptococcus* species (excluding enterococci), *E coli*, *Proteus mirabilis*, *Neisseria gonorrhoeae*, *Bacteroides* species (excluding *B distasonis*, *B ovatus*, *B thetaiotaomicron*), *Fusobacterium* species,† and gram-positive anaerobic cocci (including *Peptococcus* and *Peptostreptococcus* species†).

Intra-abdominal infections caused by *E coli*, *Klebsiella* species (including *K pneumoniae*†), *Streptococcus* species (excluding enterococci), and *Bacteroides* species (excluding *B distasonis*, *B ovatus*, *B thetaiotaomicron*).

Bone and joint infections caused by *Staphylococcus aureus*.†

***NOTE:** Some strains of *Staphylococcus epidermidis* are resistant to cefotetan.

†Efficacy for this organism in this organ system was studied in fewer than ten infections.

PROPHYLAXIS: The preoperative administration of CEFOTAN may reduce the incidence of certain postoperative infections in patients undergoing surgical procedures that are classified as clean contaminated or potentially contaminated (eg, cesarean section, abdominal or vaginal hysterectomy, transurethral surgery, biliary tract surgery, and gastrointestinal surgery).

The prophylactic dose of CEFOTAN should be administered 30 to 60 minutes prior to surgery. In patients undergoing cesarean section, CEFOTAN should be administered intravenously after the clamping of the umbilical cord.

If there are signs and symptoms of infection, specimens for culture should be obtained for identification of the causative organism so that appropriate therapeutic measures may be initiated.

CONTRAINDICATIONS
CEFOTAN is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

WARNINGS
Before therapy with CEFOTAN is instituted, careful inquiry should be made to determine whether the patient has had previous hypersensitivity reactions to cefotetan disodium, cephalosporins, penicillins, or other drugs. This product should be given cautiously to penicillin-sensitive patients. Antibiotics should be administered with caution to any patient who has demonstrated some form of allergy, particularly to drugs. If an allergic reaction to CEFOTAN occurs, discontinue the drug. Serious acute hypersensitivity reactions may require epinephrine and other emergency measures.

Pseudomembranous colitis has been reported with the use of cephalosporins (and other broad-spectrum antibiotics); therefore, it is important to consider its diagnosis in patients who develop diarrhea in association with antibiotic use.

Treatment with broad-spectrum antibiotics may alter normal flora of the colon and may permit overgrowth of clostridia. Studies indicate a toxin produced by *Clostridium difficile* is one primary cause of antibiotic-associated colitis. Cholestyramine and colestipol resins have been shown to bind the toxin in vitro.

Mild cases of colitis may respond to drug discontinuance alone. Moderate to severe cases should be managed with fluid, electrolyte, and protein supplementation as indicated. When the colitis is not relieved by drug discontinuance, or when it is severe, oral vancomycin is the treatment of choice for antibiotic-associated pseudomembranous colitis produced by *C difficile*. Other causes should also be considered.

PRECAUTIONS
GENERAL: As with other broad-spectrum antibiotics, prolonged use of CEFOTAN may result in overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection does occur during therapy, appropriate measures should be taken.

In common with many other broad-spectrum antibiotics, CEFOTAN may be associated with a fall in prothrombin activity. Those at risk include patients with renal or hepatic impairment, or poor nutritional state. Prothrombin times should be monitored in patients at risk and exogenous Vitamin K administered as indicated.

CEFOTAN should be used with caution in individuals with a history of gastrointestinal disease, particularly colitis.

INFORMATION FOR PATIENTS: As with some other cephalosporins, a disulfiram-like reaction characterized by flushing, sweating, headache, and tachycardia may occur when alcohol (beer, wine, etc) is ingested within 72 hours after CEFOTAN administration. Patients should be cautioned about the ingestion of alcoholic beverages following the administration of CEFOTAN.

DRUG INTERACTIONS: If CEFOTAN and an aminoglycoside are used concomitantly, renal function should be carefully monitored, especially if higher dosages of the aminoglycoside are to be administered or if therapy is prolonged, because of the potential nephrotoxicity and ototoxicity of aminoglycoside antibiotics. Although, to date, nephrotoxicity has not been noted when CEFOTAN was given alone, it is possible that nephrotoxicity may be potentiated if CEFOTAN is used concomitantly with an aminoglycoside.

DRUG/LABORATORY TEST INTERACTIONS: A false positive reaction for glucose in urine may occur with Benedict's or Fehling's solution.

As with other cephalosporins, high concentrations of cefotetan may interfere with measurement of serum and urine creatinine levels of Jaffe reaction and produce false increases in the levels of creatinine reported.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY: Although long-term studies in animals have not been performed to evaluate carcinogenic potential, no mutagenic potential of cefotetan was found in standard laboratory tests.

Cefotetan has adverse effects on the testes of prepubertal rats. Subcutaneous administration of 500 mg/kg/day (approx 8-16 times the usual adult human dose) on days 6-35 of life (thought to be developmentally analogous to late childhood and prepuberty in humans) resulted in reduced testicular weight and seminiferous tubule degeneration in 10 of 10 animals. Affected cells included spermatogonia and spermatocytes; Sertoli and Leydig cells were unaffected. Incidence and severity of lesions were dose-dependent; at 120 mg/kg/day (approx 2-4 times the usual human dose), only 1 of 10 treated animals was affected, and the degree of degeneration was mild. Similar lesions have been observed in experiments of comparable design with other methylthiotetrazole-containing antibiotics and impaired fertility has been reported, particularly at high dose levels. No testicular effects were observed in 7-week-old rats treated with up to 1000 mg/kg/day SC for 5 weeks, or in infant dogs (3 weeks old) that received up to 300 mg/kg/day IV for 5 weeks. The relevance of these findings to humans is unknown.

USAGE IN PREGNANCY: Pregnancy Category B: Reproduction studies have been performed in rats and monkeys at doses up to 20 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to cefotetan. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

USAGE IN NURSING MOTHERS: Cefotetan is excreted in human milk in very low concentrations. Caution should be exercised when cefotetan is administered to a nursing woman.

PEDIATRIC USE: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS
In clinical studies the following adverse effects were considered related to CEFOTAN therapy.

Gastrointestinal symptoms occurred in 1.5 percent of patients; the most frequent were diarrhea (1 in 80) and nausea (1 in 700).

Hematologic laboratory abnormalities occurred in 1.4 percent of patients and included eosinophilia (1 in 200), positive direct Coombs' test (1 in 250), and thrombocytosis (1 in 300).

Hepatic enzyme elevations occurred in 1.2 percent of patients and included a rise in SGPT (1 in 150), SGOT (1 in 300), alkaline phosphatase (1 in 700), and LDH (1 in 700).

Hypersensitivity reactions were reported in 1.2 percent of patients and included rash (1 in 150) and itching (1 in 700).

Local effects were reported in less than one percent of patients and included phlebitis at the site of injection (1 in 300), and discomfort (1 in 500).

DOSAGE AND ADMINISTRATION
TREATMENT: The usual adult dosage is 1 or 2 grams of CEFOTAN administered intravenously or intramuscularly every 12 hours for 5 to 10 days. Proper dosage and route of administration should be determined by the condition of the patient, severity of the infection, and susceptibility of the causative organism.

GENERAL GUIDELINES FOR DOSAGE OF CEFOTAN

Type of Infection	Daily Dose	Frequency and Route
Urinary Tract	1-4 grams	500 mg every 12 hours IV or IM 1 or 2 g every 24 hours IV or IM 1 or 2 g every 12 hours IV or IM
Other Sites	2-4 grams	1 or 2 g every 12 hours IV or IM
Severe	4 grams	2 g every 12 hours IV
Life-Threatening	6* grams	3 g every 12 hours IV

*Maximum daily dosage should not exceed 6 grams.

PROPHYLAXIS: To prevent postoperative infection in clean contaminated or potentially contaminated surgery in adults, the recommended dosage is 1 or 2 g of CEFOTAN administered once, intravenously, 30 to 60 minutes prior to surgery. In patients undergoing cesarean section, the dose should be administered as soon as the umbilical cord is clamped.

IMPAIRED RENAL FUNCTION: When renal function is impaired, a reduced dosage schedule must be employed. The following dosage guidelines may be used.

DOSAGE GUIDELINES FOR PATIENTS WITH IMPAIRED RENAL FUNCTION

Creatinine Clearance mL/min	Dose	Frequency
>30	Usual Recommended Dose*	Every 12 hours
10-30	Usual Recommended Dose*	Every 24 hours
<10	Usual Recommended Dose*	Every 48 hours

*Dose determined by the type and severity of infection, and susceptibility of the causative organism.

Cefotetan is dialyzable and it is recommended that for patients undergoing intermittent hemodialysis, one-quarter of the usual recommended dose be given every 24 hours on days between dialysis and one-half the usual recommended dose on the day of dialysis.

HOW SUPPLIED
CEFOTAN is a dry, white to pale yellow powder supplied in vials containing cefotetan disodium equivalent to 1 g and 2 g cefotetan activity for intravenous and intramuscular administration. The 1 g dose is available in 10 mL and 100 mL vials, and the 2 g dose is available in 20 mL and 100 mL vials. The vials should not be stored at temperatures above 22°C and should be protected from light.
1 g in 10 mL vial (NDC 0038-0376-10)
2 g in 20 mL vial (NDC 0038-0377-20)
1 g in 100 mL vial (NDC 0038-0376-11)
2 g in 100 mL vial (NDC 0038-0377-21)

Manufactured for

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Wilmington, Delaware 19897

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CONTRIBUTIONS. Four typed copies of the manuscript and four copies of the illustrations should be sent prepaid to the Chairman of the Editorial Board of Annals of Surgery.

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Department of Surgery
Duke University Medical Center
Durham, North Carolina 27710

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Type manuscript double spaced, including title page, abstract, text, acknowledgments, references, tables, and legends.

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Submit the required number of copies of manuscript and figures (*see* journal's instructions) in heavy-paper envelope. Submitted manuscript should be accompanied by covering letter, as described under "Submission of Manuscripts," and permissions to reproduce previously published materials or to use illustrations that may identify subjects.

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Type manuscript on white bond paper, 20.3 by 26.7 cm or 21.6 by 27.9 cm (8 by 10½ in. or 8½ by 11 in.) or ISO A4 (212 by 297 mm) with margins of at least 2.5 cm (1 in.). Use double spacing throughout, including title page, abstract, text, acknowledgments, references, tables, and legends for illustrations. Begin each of the following sections on separate pages: title page, abstract and key words, text, acknowledgments, references, individual tables, and legends. Number pages consecutively, beginning with the title page. Type the page number in the upper right-hand corner of each page.

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The second page should carry an abstract of not more than 150 words. The abstract should state the purposes of the study or investigation, basic procedures (study subjects or experimental animals and observational and analytic methods), main findings (give specific data and their statistical significance, if possible), and the principal conclusions. Emphasize new and important aspects of the study or observations. Use only approved abbreviations (*see* list of Commonly Used Approved Abbreviations elsewhere in this document).

Key (indexing) terms: Below the abstract, provide and identify as such, three to 10 key words or short phrases that will assist indexers in cross-indexing your article and that may be published with the abstract. Use terms from the Medical Subject Headings list from *Index Medicus* whenever possible.

TEXT

The text of observational and experimental articles is usually—but not necessarily—divided into sections with the headings Introduction, Methods, Results, and Discussion. Long articles may need subheadings within some sections to clarify their content, especially the Results and Discussion sections. Other types of articles such as case reports, reviews, and editorials are likely to need other formats, and authors should consult individual journals for further guidance.

Introduction: Clearly state the *purpose* of the article. Summarize the rationale for the study or observation. Give only strictly pertinent references, and do not review the subject extensively.

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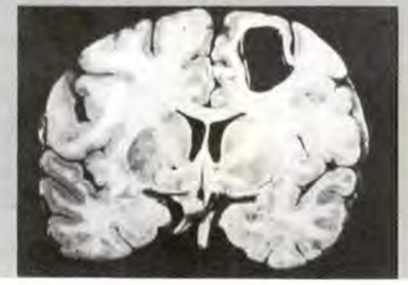

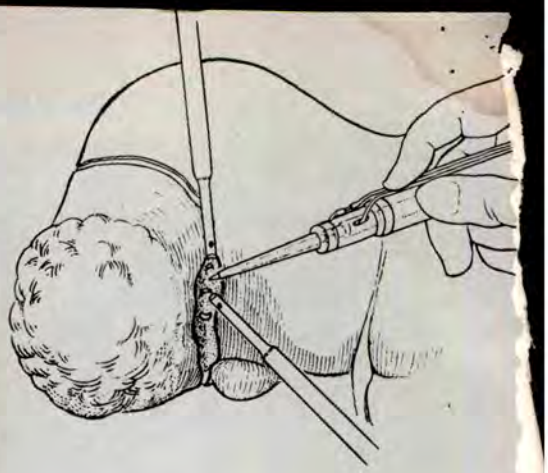

SURGICAL TREATMENT of METASTATIC CANCER

Edited by Steven A. Rosenberg, M.D., Ph.D.

Chief of Surgery, National Cancer Institute, Bethesda, MD.

9 contributors.

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with acetaminophen 500 mg

INDICATIONS AND USAGE: For the relief of moderate to moderately severe pain.

CONTRAINDICATIONS: Hypersensitivity to acetaminophen or hydrocodone.

WARNINGS

Drug Abuse and Dependence: VICODIN is subject to the Federal Controlled Substances Act (Schedule III). Psychic dependence, physical dependence and tolerance may develop upon repeated administration of narcotics; therefore, VICODIN should be prescribed and administered with the same caution appropriate to the use of other oral-narcotic-containing medications.

Respiratory Depression: At high doses or in sensitive patients, hydrocodone may produce dose-related respiratory depression by acting directly on brain stem respiratory centers. Hydrocodone also affects centers that control respiratory rhythm, and may produce irregular and periodic breathing.

Head Injury and Increased Intracranial Pressure: The respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a preexisting increase in intracranial pressure. Furthermore, narcotics produce adverse reactions which may 'obscure the clinical course of patients with head injuries.

Acute Abdominal Conditions: The administration of narcotics may obscure the diagnosis or clinical course of patients with acute abdominal conditions.

PRECAUTIONS

Special Risk Patients: VICODIN should be used with caution in elderly or debilitated patients and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, prostatic hypertrophy or urethral stricture.

Information for Patients: VICODIN, like all narcotics, may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery; patients should be cautioned accordingly.

Cough Reflex: Hydrocodone suppresses the cough reflex; caution should be exercised when VICODIN is used postoperatively and in patients with pulmonary disease.

Drug Interactions: The CNS-depressant effects of VICODIN may be additive with that of other CNS depressants. When combined therapy is contemplated, the dose of one or both agents should be reduced. The use of MAO inhibitors or tricyclic antidepressants with hydrocodone preparations may increase the effect of either the antidepressant or hydrocodone. The concurrent use of anticholinergics with hydrocodone may produce paralytic ileus.

Usage in Pregnancy: Pregnancy Category C. Hydrocodone has been shown to be teratogenic in hamsters when given in doses 700 times the human dose. There are no adequate and well-controlled studies in pregnant women. VICODIN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects: Babies born to mothers who have been taking opioids regularly prior to delivery will be physically dependent. The intensity of the syndrome does not always correlate with the duration of maternal opioid use or dose.

Labor and Delivery: Administration of VICODIN to the mother shortly before delivery may result in some degree of respiratory depression in the newborn, especially if higher doses are used.

Nursing Mothers: It is not known whether this drug is excreted in human milk; therefore, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Central Nervous System: Sedation, drowsiness, mental clouding, lethargy, impairment of mental and physical performance, anxiety, fear, dysphoria, dizziness, psychic dependence, mood changes.

Gastrointestinal System: Nausea and vomiting may occur; they are more frequent in ambulatory than in recumbent patients. Prolonged administration of VICODIN may produce constipation.

Genitourinary System: Ureteral spasm, spasm of vesical sphincters and urinary retention have been reported.

Respiratory Depression: (See WARNINGS.)

DOSAGE AND ADMINISTRATION: Dosage should be adjusted according to the severity of the pain and the response of the patient. However, tolerance to hydrocodone can develop with continued use, and the incidence of untoward effects is dose related. The usual dose is one tablet every six hours as needed for pain. (If necessary, this dose may be repeated at four-hour intervals.) In cases of more severe pain, two tablets every six hours (up to eight tablets in 24 hours) may be required.

Revised, April 1982 5685

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	CONSTIPATION	RESPIRATORY DEPRESSION	SEDATION	EMESIS	PHYSICAL DEPENDENCE
HYDROCODONE		X			X
CODEINE	X	X	X	X	X
OXYCODONE	XX	XX	XX	XX	XX

Blank space indicates that no such activity has been reported.

Table adapted from Facts and Comparisons (Nov.) 1984 and Catalano RB. The medical approach to management of pain caused by cancer. "Semin Oncol" 1975; 2; 379-92 and Reuler JB, et. al. The chronic pain syndrome: misconceptions and management. "Ann Intern Med" 1980; 93; 588-96.

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1. Hopkinson JH III: *Curr Ther Res* 24: 503-516, 1978
2. Beaver, WT *Arch Intern Med,* 141:293-300, 1981.

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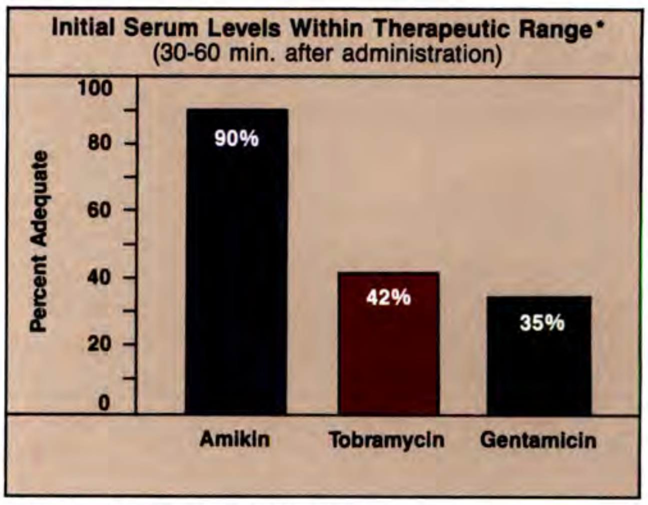
First-Dose Predictability.

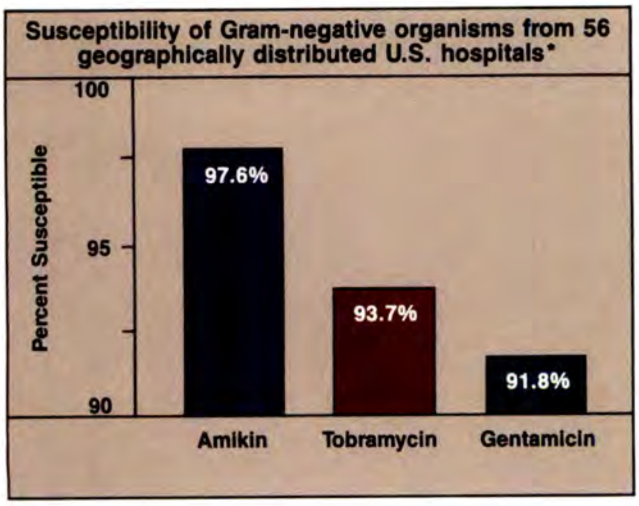
After the first dose, Amikin produces therapeutic blood levels that are more predictable than those of the other aminoglycosides.[1]



*Adapted from Holloway WJ: Management of sepsis in the elderly. *Am J Med* 80 (suppl 6B): 143-148, 1986.

First-Dose Antimicrobial Activity.

Amikin has the broadest spectrum of any aminoglycoside.[2]



Total Amikin isolates = 247,503

*In vitro data may not be directly correlated to clinical effectiveness. Data on file, Bristol Laboratories.

First-Dose Synergy.

In combination with antipseudomonal penicillins and latest generation cephalosporins, Amikin is overall the most synergistic of the aminoglycosides.[3,4]

First-Dose Economy.

The least expensive aminoglycoside is not necessarily the one with the lowest acquisition cost. It's the one *not* requiring replacement with a more effective agent.[5]

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AMIKIN®

AMIKACIN SULFATE

BRIEF SUMMARY OF PRESCRIBING INFORMATION (1) 10/83

For complete prescribing information, please consult product literature.

WARNINGS

Patients treated with aminoglycosides should be under close clinical observation because of the potential ototoxicity and nephrotoxicity associated with their use.

Ototoxicity, both auditory and vestibular, can occur in patients treated at higher doses or for periods longer than those recommended. The risk of amikacin-induced ototoxicity is greater in patients with renal damage. High frequency deafness usually occurs first and can be detected only by audiometric testing. Vertigo may occur and may be evidence of vestibular injury.

The ototoxicity potential of amikacin in infants is not known. Until more safety reports become available, amikacin should be used in infants only in those specific circumstances when susceptibility testing indicates that other aminoglycosides cannot be used or are otherwise contraindicated, and when the infant can be observed closely for evidence of toxicity.

Aminoglycosides are potentially nephrotoxic. Renal and eighth-nerve function should be closely monitored in patients with known or suspected renal impairment and also in those whose renal function is initially normal but who develop signs of renal dysfunction during therapy. Such impairment may be characterized by decreased creatinine clearance, the presence of cells or casts, oliguria, proteinuria, decreased urine specific gravity or evidence of increasing nitrogen retention (increasing BUN or creatinine).

Evidence of impairment in renal, vestibular or auditory function requires discontinuation of the drug or dosage adjustment.

Serum concentrations should be monitored when feasible, and prolonged peak concentrations above 35 mcg/ml should be avoided. Urine should be examined for increased excretion of protein, the presence of cells and casts, and decreased specific gravity.

Concurrent and/or sequential use of topically or systemically neurotoxic or nephrotoxic antibiotics, particularly kanamycin, gentamicin, tobramycin, neomycin, streptomycin, cephaloridine, paromomycin, viomycin, polymyxin B, colistin and vancomycin should be avoided.

AMIKIN should not be given concurrently with potent diuretics (ethacrynic acid, furosemide, meralluride sodium, sodium mercaptomerin or mannitol). Some diuretics themselves cause ototoxicity, and intravenously administered diuretics enhance aminoglycoside toxicity by altering antibiotic concentrations in serum and tissue.

CONTRAINDICATIONS

A history of hypersensitivity to amikacin is a contraindication for its use.

WARNINGS

See "Warning" box above.

PRECAUTIONS

AMIKIN is potentially nephrotoxic, ototoxic, and neurotoxic. The concurrent or serial use of other ototoxic or nephrotoxic agents should be avoided either systemically or topically because of the potential for additive effects. Such agents include antibacterial drugs such as kanamycin, gentamicin, tobramycin, neomycin, streptomycin, cephaloridine, paromomycin, viomycin, polymyxin B, colistin and vancomycin as well as certain diuretic agents such as ethacrynic acid or furosemide.

Ototoxicity — See "Warning" box.

Nephrotoxicity — Since AMIKIN is present in high concentrations in the renal excretory system, patients should be well hydrated to minimize chemical irritation of the renal tubules. Kidney function should be assessed by the usual methods prior to starting therapy and daily during the course of treatment.

If signs of renal irritation appear (casts, white or red cells or albumin), hydration should be increased. A reduction in dosage (see "Dosage and Administration") may be desirable if other evidence of renal dysfunction occurs such as decreased creatinine clearance, decreased urine specific gravity, increased BUN, creatinine or oliguria. If azotemia increases or if a progressive decrease in urinary output occurs, treatment should be stopped.

Note: When patients are well hydrated and kidney function is normal the risk of nephrotoxic reactions with amikacin is low if the dosage recommendations (see "Dosage and Administration") are not exceeded.

Neurotoxicity — Neuromuscular blockade and muscular paralysis have been demonstrated in the cat with high doses of amikacin (188 mg/Kg). The possibility of neuromuscular blockade and respiratory paralysis should be considered when amikacin is administered concomitantly with anesthetic or neuromuscular blocking drugs. If blockade occurs, calcium salts may reverse this phenomenon.

Other — Cross-allergenicity among aminoglycosides has been demonstrated. As with other antibiotics the use of amikacin may result in overgrowth of nonsusceptible organisms. If this occurs, appropriate therapy should be instituted.

Pregnancy — Reproduction studies have been performed in rats and mice and have revealed no evidence of impaired fertility or harm to the fetus due to amikacin. There are no well-controlled studies in pregnant women but investigational experience does not include any positive evidence of adverse effects on the fetus. Although there is no clearly defined risk, such experience cannot exclude the possibility of infrequent or subtle damage to the fetus. AMIKIN should be used in pregnant women only when clearly needed.

It is not known whether this drug is excreted in human milk. As a general rule, nursing should not be undertaken while a patient is on a drug since many drugs are excreted in human milk.

ADVERSE REACTIONS

Ototoxicity — See "Warning" box.

Nephrotoxicity — Albuminuria, presence of red and white cells, casts, azotemia and oliguria have been reported.

Other — In addition to those described above, other adverse reactions which have been reported on rare occasions are skin rash, drug fever, headache, paresthesia, tremor, nausea and vomiting, eosinophilia, arthralgia, anemia, hypotension.

Overdosage — In the event of overdosage or toxic reaction, peritoneal dialysis or hemodialysis will aid in the removal of amikacin from the blood.

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"I'D LIKE TO MAKE AN APPOINTMENT WITH THE DOCTOR"

Be prepared, Doctor. More patients will be asking about colorectal cancer. According to a survey* conducted by the American Cancer Society, many people would like to receive more information about colorectal cancer, and 83% said they would want to be checked for it. Further, they are learning that this cancer can be detected *before* symptoms appear. The present cure rate is 44%. The cure rate *could* be as high as 75%, with early detection and appropriate management.

For asymptomatic persons the Society recommends annual digital rectal examination at age 40 and over; at age 50 and over, an annual stool blood test, as well as sigmoidoscopy every three to five years, following two initial annual negative sigmoidoscopies.

We're here to help. You can reach us at your local American Cancer Society office or write to our Professional Education Department at National Headquarters, 90 Park Avenue, New York, N.Y. 10016. Ask about the Society's Colorectal Check program of professional and public education for the early detection of colorectal cancer.

AMERICAN CANCER SOCIETY®

*"Cancer of the Colon and Rectum: Summary of Public Attitude Survey," *Ca* 33:359-365, 1983 (Nov.-Dec.).

THROMBOSTAT™ (THROMBIN, USP), a trusted hemostatic aid, is now available in a pump spray form—permitting flexible and easy application. With the new THROMBOSTAT pump, you can achieve hemostasis in seconds over large body surface areas. Each depression of the pump offers an even distribution

SPRAY ON HEMOSTASIS

of THROMBOSTAT solution—allowing uniform hemostasis of the total area. The THROMBOSTAT pump is available in a convenient sterile kit that features a 20,000-unit vial of THROMBOSTAT (a practical size for procedures involving capillary bleeding), an appropriate measure of diluent, and a pump sprayer cap. The kit offers sterile packaging—permitting the entire contents to be brought directly into the sterile field. With the new THROMBOSTAT kit, it has never been simpler to control capillary bleeding.

Please see next page for brief summary of prescribing information.

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PD-34-JA-2352-P-1A (3-85)

THROMBOSTAT™ (THROMBIN, USP) (Bovine Origin)

Before prescribing, please see full prescribing information. A Brief Summary follows:

Thrombostat must not be injected! Apply on the surface of bleeding tissue as a solution or powder.

INDICATIONS AND USAGE: Thrombostat (Thrombin, USP) is indicated as an aid in hemostasis wherever oozing blood from capillaries and small venules is accessible.

In various types of surgery solutions of Thrombostat may be used in conjunction with Absorbable Gelatin Sponge, USP for hemostasis.

CONTRAINDICATIONS: Thrombostat is contraindicated in persons known to be sensitive to any of its components and/or to material of bovine origin.

WARNING: Because of its action in the clotting mechanism, Thrombostat must not be injected or otherwise allowed to enter large blood vessels. Extensive intravascular clotting and even death may result. Thrombostat is an antigenic substance and has caused sensitivity and allergic reactions when injected into animals.

PRECAUTIONS: General: Consult the absorbable gelatin sponge product labeling for complete information for use prior to utilizing the thrombin-saturated-sponge procedure.

Pregnancy—Teratogenic effects: Pregnancy Category C. Animal reproduction studies have not been conducted with Thrombin, Topical (Bovine). It is also not known whether Thrombin, Topical (Bovine) can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Thrombin, Topical (Bovine) should be given to a pregnant woman only if clearly indicated.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: An allergic type reaction following the use of Thrombostat for treatment of epistaxis has been reported. Febrile reactions have also been observed following the use of Thrombostat in certain surgical procedures but no cause-effect relationship has been established.

DOSAGE AND ADMINISTRATION: General: Solutions of Thrombostat may be prepared in sterile distilled water or isotonic saline. The intended use determines the strength of the solution to prepare. For general use in plastic surgery, dental extractions, skin grafting, neurosurgery, etc, solutions containing approximately 100 units per ml are frequently used. For this, 10 ml of diluent added to the 1000 unit package is suitable. Where bleeding is profuse, as from cut surfaces of liver and spleen, concentrations as high as 1000 to 2000 units per ml may be required. For this the 5000 unit vial dissolved in 5 ml or 2.5 ml respectively, of the diluent supplied in the package is convenient. Intermediate strengths to suit the needs of the case may be prepared by selecting the proper strength package and dissolving the contents in an appropriate volume of diluent. In many situations, it may be advantageous to use Thrombostat (Thrombin, USP) in dry form on oozing surfaces.

Caution: Solutions should be used the day they are prepared. The solution may be used for up to 6 hours when stored at room temperature; up to 24 hours when stored under refrigeration, and, if necessary, up to 48 hours when stored frozen.

The following techniques are suggested for the topical application of Thrombostat.

1. The recipient surface should be sponged (not wiped) free of blood before Thrombostat is applied.
2. A spray may be used or the surface may be flooded using a sterile syringe and small gauge needle. The most effective hemostasis results when the Thrombostat mixes freely with the blood as soon as it reaches the surface.
3. In instances where Thrombostat in dry form is needed, the vial is opened by removing the metal ring by flipping up the plastic cap and tearing counterclockwise. The rubber-diaphragm cap may be easily removed and the dried Thrombostat is then broken up into a powder by means of a sterile glass rod or other suitable sterile instrument.
4. Sponging of treated surfaces should be avoided in order that the clot remain securely in place.

Thrombostat may be used in conjunction with Absorbable Gelatin Sponge, USP as follows:

1. Prepare Thrombostat solution of the desired strength.
2. Immerse sponge strips of the desired size in the Thrombostat solution. Knead the sponge strips vigorously with moistened gloved fingers to remove trapped air, thereby facilitating saturation of the sponge.
3. Apply saturated sponge to bleeding area. Hold in place for 10 to 15 seconds with a pledget of cotton or a small gauze sponge.

Thrombostat Kit: Thrombostat Kit contains one sterile 20,000 unit vial of Thrombostat, one sterile vial of Isotonic Saline Diluent, and one sterile pump sprayer cap. The Kit may be used as follows:

1. Remove the Tyvek blister lid by pulling up at the indicated corner. The sterile inner tray can be lifted out or introduced into the operating field.
2. The cover to the sterile inner tray is removed by pulling up on the finger tab, exposing the sterile contents.
3. Thrombostat solution of the desired strength is prepared and the pump sprayer cap inserted and seated on the Thrombostat solution vial. Note: Several strokes of the pump sprayer will be required before the Thrombostat solution is expelled.
4. Alternatively, when Thrombostat in dry form is needed, the vial is opened as described above and the dried Thrombostat broken up into a powder by means of a sterile glass rod or other suitable sterile instrument. **4173G014**

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FIGHT CANC
BEFORE YO
GET IT.

OR AFTER
YOU GET IT.

It's a lot easier to fight cancer before you get it.

Scientists estimate that up to
of all cancer could be prevented

By simply making a few chan
in your lifestyle.

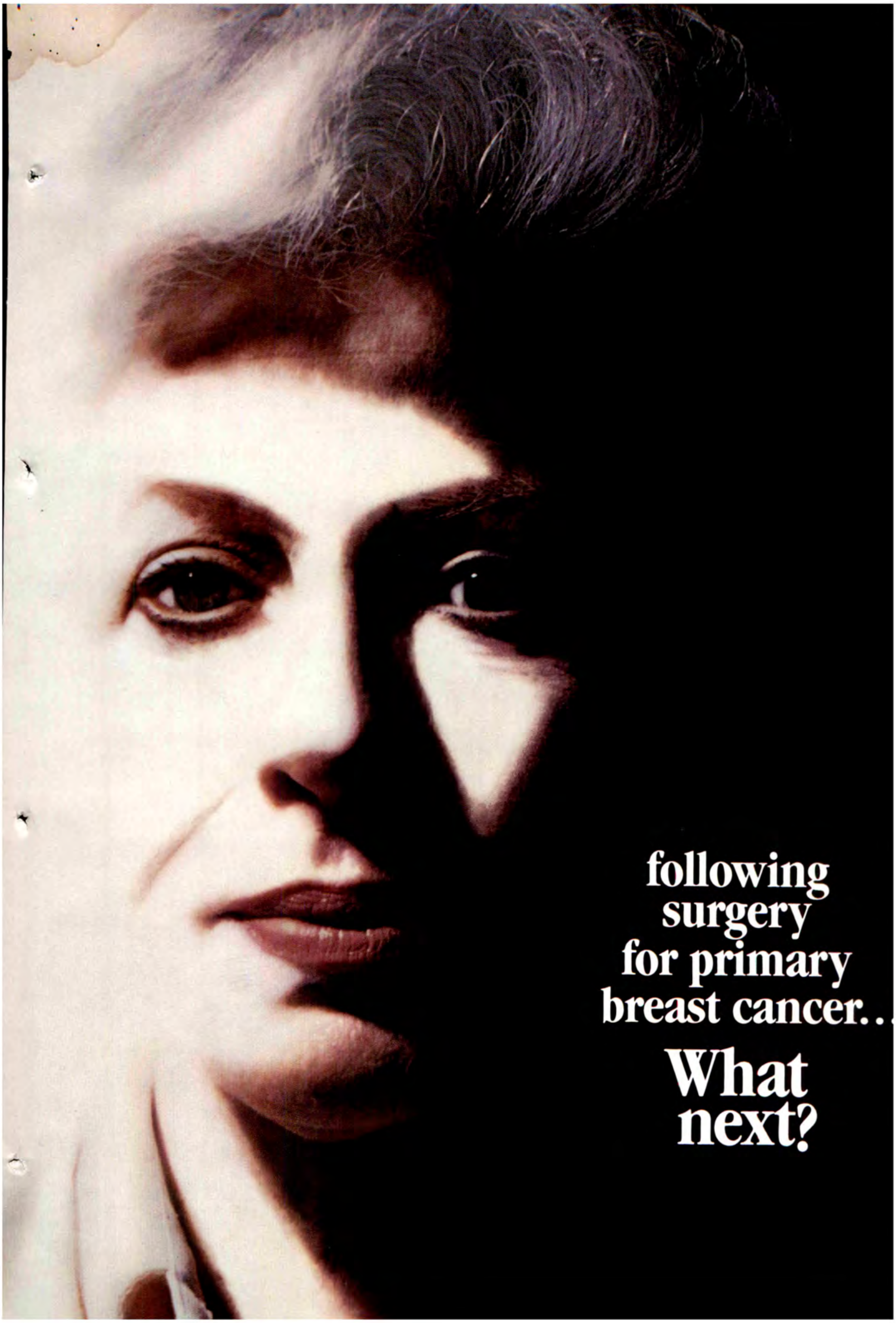
By not getting too much sun.
not smoking cigarettes. By not
overeating. And by following a
high in fiber and low in fat.

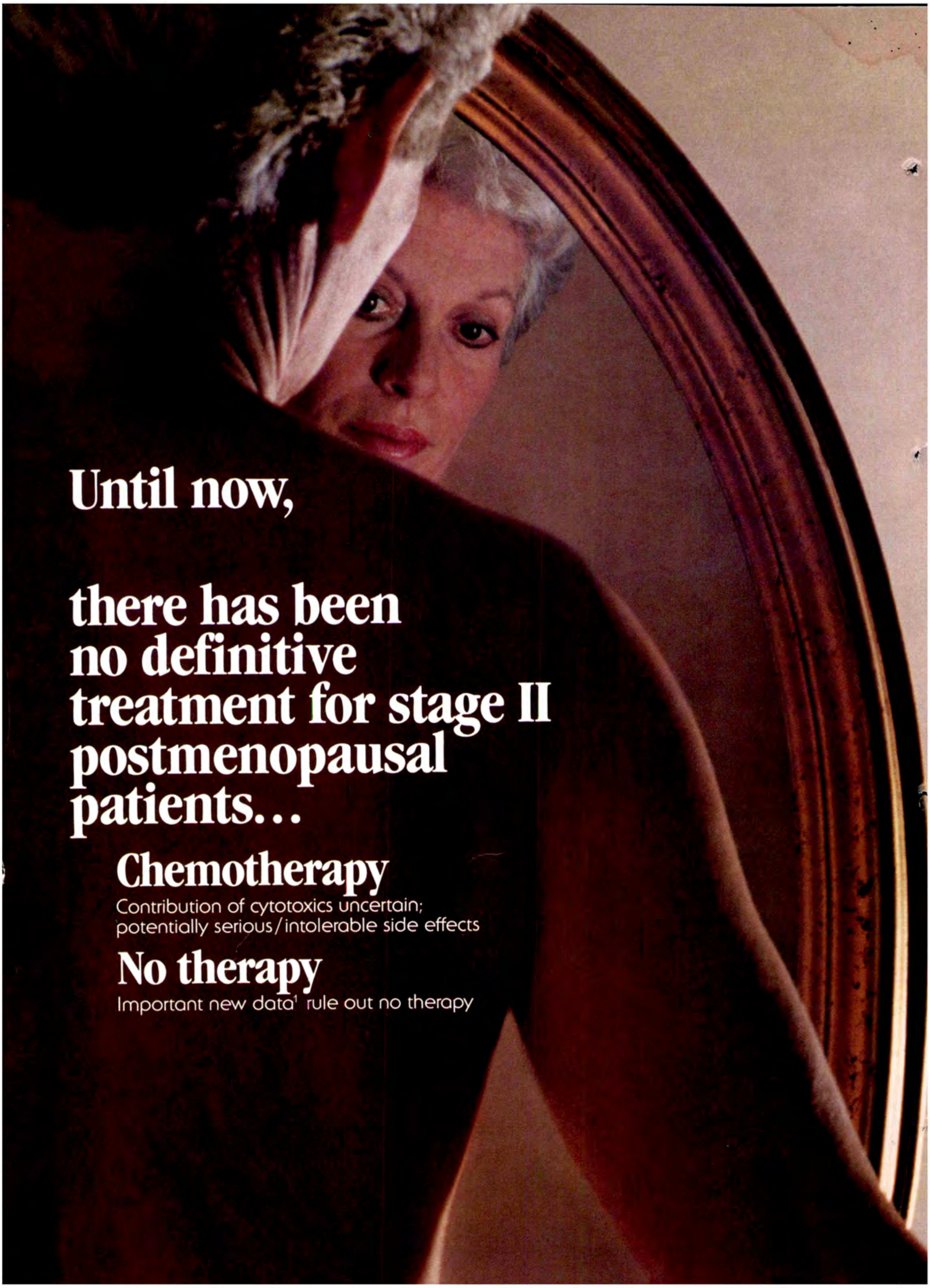
By simply doing these few thi
you could drastically reduce yo
risk of getting cancer.

Sure, you could still get cancer.

But why not give yourself the odds against it?

AMERIC
CANCER
SOCIETY
Help us keep win


following surgery for primary breast cancer...
What next?


Until now,
there has been no definitive treatment for stage II postmenopausal patients...
Chemotherapy
Contribution of cytotoxics uncertain; potentially serious/intolerable side effects
No therapy
Important new data[1] rule out no therapy

Today there is.

10 MG TABLETS

Nolvadex®

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Adjuvant Monotherapy

Now, the treatment of choice

A recent National Institutes of Health consensus report states that following surgery, "Tamoxifen [NOLVADEX] should now be regarded as standard therapy for postmenopausal patients with positive axillary lymph nodes and positive hormone receptor status."[1]

NOLVADEX increases disease-free time[2-5] by delaying recurrence following total mastectomy and axillary dissection in postmenopausal women with breast cancer (T_{1-3}, N_1, M_0). Moreover, NOLVADEX improves overall survival, with a 34% reduction in risk of mortality, as observed in the NOLVADEX Adjuvant Trial Organization (NATO) study.[4] This treatment is extremely well tolerated by patients[2-5]; in fact, one double-blind, placebo-controlled study demonstrated a NOLVADEX side effects profile similar to placebo.[2] And, since NOLVADEX has a mild side effects profile and is easy to administer, patients are afforded a better quality of life. NOLVADEX—today's promising breast cancer therapy for the postmenopausal woman—in the adjuvant setting and in metastatic disease.

Please see next page for brief summary of prescribing information.

STUART PHARMACEUTICALS
Division of ICI Americas Inc
Wilmington, Delaware 19897

10 MG TABLETS

Nolvadex®

TAMOXIFEN CITRATE

BRIEF SUMMARY

INDICATIONS AND USAGE: NOLVADEX is effective in the treatment of metastatic breast cancer in postmenopausal women. Available evidence indicates that patients whose tumors are estrogen receptor positive are more likely to benefit from NOLVADEX therapy.

NOLVADEX is effective in delaying recurrence following total mastectomy and axillary dissection in postmenopausal women with breast cancer (T1-3, N1, M0). The estrogen and progesterone receptor values may help to predict whether NOLVADEX therapy is likely to be beneficial. In some NOLVADEX adjuvant studies, most of the benefit to date has been in the subgroup with 4 or more positive axillary nodes.

CONTRAINDICATIONS: None known.

WARNINGS: Pregnancy Category D: NOLVADEX may cause fetal harm when administered to a pregnant woman. Individuals should not become pregnant while taking NOLVADEX. Effects on reproductive functions are expected from the antiestrogenic properties of the drug. In reproductive studies in rats at dose levels equal to or below the human dose, nonteratogenic developmental skeletal changes were seen and were found to be reversible. In addition, in fertility studies in rats and in teratology studies in rabbits using doses at or below those used in humans, a lower incidence of embryo implantation and a higher incidence of fetal death or retarded in utero growth were observed, with slower learning behavior in some rat pups. The impairment of learning behavior did not achieve statistical significance in one study, and, in another study where significance was reported, this was by comparing dosed animals with controls of another study. Several pregnant marmosets were dosed during organogenesis or in the last half of pregnancy. No deformations were seen and although the dose was high enough to terminate pregnancy in some animals, those that did maintain pregnancy showed no evidence of teratogenic malformations. There are no adequate and well-controlled studies in pregnant women. There have been reports of spontaneous abortions, birth defects, fetal deaths, and vaginal bleeding. If this drug is used during pregnancy or the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

Ocular changes have been reported in a few patients who, as part of a clinical trial, were treated for periods greater than one year with NOLVADEX at doses at least four times the highest recommended daily dose of 40 mg. The ocular changes consist of retinopathy and, in some patients, there are also corneal changes and a decrease in visual acuity.

In addition, a few cases of ocular changes including visual disturbance, corneal changes, and/or retinopathy have been reported in patients treated with NOLVADEX at recommended doses. It is uncertain if these effects are due to NOLVADEX.

As with other additive hormonal therapy (estrogens and androgens), hypercalcemia has been reported in some breast cancer patients with bone metastases within a few weeks of starting treatment with NOLVADEX. If hypercalcemia does occur, appropriate measures should be taken and, if severe, NOLVADEX should be discontinued.

PRECAUTIONS: General: NOLVADEX should be used cautiously in patients with existing leukopenia or thrombocytopenia. Observations of leukopenia and thrombocytopenia occasionally have been made, but it is uncertain if these effects are due to NOLVADEX therapy. Transient decreases in platelet counts, usually to 50,000-100,000/cu mm, infrequently lower, have been occasionally reported in patients taking NOLVADEX for breast cancer. No hemorrhagic tendency has been recorded and the platelet counts returned to normal levels even though treatment with NOLVADEX continued.

Laboratory Tests: Periodic complete blood counts, including platelet counts, may be appropriate.

Carcinogenesis: While no conventional bioassay has been conducted, endocrine changes in immature and mature mice were investigated in a 13-month study. Granulosa cell ovarian tumors and interstitial cell testicular tumors were found in mice receiving NOLVADEX, but not in the controls.

Mutagenesis: No genotoxic potential has been found in a battery of in vivo and in vitro tests with pro- and eukaryotic test systems with drug metabolizing systems present.

Impairment of Fertility: Fertility in female rats was decreased following administration of 0.04 mg/kg for 2 weeks prior to mating through day 7 of pregnancy. There was a decreased number of implantations, and all fetuses were found dead.

Following administration to rats of 0.16 mg/kg from days 7-17 of pregnancy, there were increased numbers of fetal deaths. Administration of 0.125 mg/kg to rabbits during days 6-18 of pregnancy resulted in abortion or premature delivery. Fetal deaths occurred at higher doses. There were no teratogenic changes in either rat or rabbit segment II studies. Several pregnant marmosets were dosed with 10 mg/kg/day either during organogenesis or in the last half of pregnancy. No deformations were seen, and, although the dose was high enough to terminate pregnancy in some animals, those that did maintain pregnancy showed no evidence of teratogenic malformations. Rats given 0.16 mg/kg from day 17 of pregnancy to 1 day before weaning demonstrated increased numbers of dead pups at parturition. It was reported that some rat pups showed slower learning behavior, but this did not achieve statistical significance in one study, and in another study where significance was reported, this was by comparing dosed animals with controls of another study.

The recommended daily human dose of 20-40 mg corresponds to 0.4-0.8 mg/kg for an average 50 kg woman.

Pregnancy Category D: See WARNINGS.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from NOLVADEX, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

ADVERSE REACTIONS: The most frequent adverse reactions to NOLVADEX are hot flashes, nausea and vomiting. These may occur in up to one-fourth of patients, but are rarely severe enough to require discontinuation of treatment.

Less frequently reported adverse reactions are vaginal bleeding, vaginal discharge, menstrual irregularities and skin rash. Usually these have not been of sufficient severity to require dosage reduction or discontinuation of treatment.

Increased bone and tumor pain and, also, local disease flare have occurred, which are sometimes associated with a good tumor response. Patients with increased bone pain may require additional analgesics. Patients with soft tissue disease may have sudden increases in the size of preexisting lesions, sometimes associated with marked erythema within and surrounding the lesions and/or the development of new lesions. When they occur, the bone pain or disease flare are seen shortly after starting NOLVADEX and generally subside rapidly.

Other adverse reactions which are seen infrequently are hypercalcemia, peripheral edema, distaste for food, pruritus vulvae, depression, dizziness, light-headedness and headache. There have been infrequent reports of thromboembolic events occurring during NOLVADEX therapy. Since for cancer patients in general an increased incidence of thromboembolic events is known to occur, a causal relationship to NOLVADEX remains conjectural. An increased incidence has been reported when cytotoxins are combined with NOLVADEX.

If adverse reactions are severe, it is sometimes possible to control them by a simple reduction of dosage without loss of control of the disease.

OVERDOSAGE: Acute overdosage in humans has not been reported. Signs observed at the highest doses following studies to determine LD_{50} in animals were respiratory difficulties and convulsions. No specific treatment for overdosage is known; treatment must be symptomatic.

DOSAGE AND ADMINISTRATION: One or two 10 mg tablets twice a day (morning and evening). In the three single agent adjuvant NOLVADEX studies noted above (See Clinical Pharmacology), NOLVADEX was administered for two years. The optimal duration of adjuvant therapy is not known.

HOW SUPPLIED: Tablets containing tamoxifen as the citrate in an amount equivalent to 10 mg of tamoxifen (round, biconvex, uncoated, white tablet identified with NOLVADEX 600 debossed on one side and a cameo debossed on the other side) are supplied in bottles of 60 tablets and 250 tablets. Protect from heat and light.

NDC 0038-0600

Rev 1/1/86

STUART PHARMACEUTICALS
Division of ICI Americas Inc
Wilmington, Delaware 19897

℞

Nolvadex
10 mg B.I.D.
Disp. 60 tabs

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WE HAVE ONLY GOOD THINGS TO SAY ABOUT CANCER OF THE COLON.

If detected early, the cure rate for colorectal cancer is very high. It can be as high as 75%.

Because we now know how to detect it early. And we know how to fight it once we detect it.

There are three simple checkup guidelines for men and women without symptoms.

One, get a digital exam every year. This is recommended for everyone over 40.

Two, get a stool blood test every year if you are over 50.

Three, after two initial negative tests one year apart, get a procto exam every three to five years if you are over 50.

These guidelines are the best protection against colorectal cancer you can have.

If you're not over 50, please give this information to friends and loved ones who are.

In any case, please help spread the word.

Good news doesn't always travel fast.

AMERICAN CANCER SOCIETY®

Get a checkup. Life is worth it.

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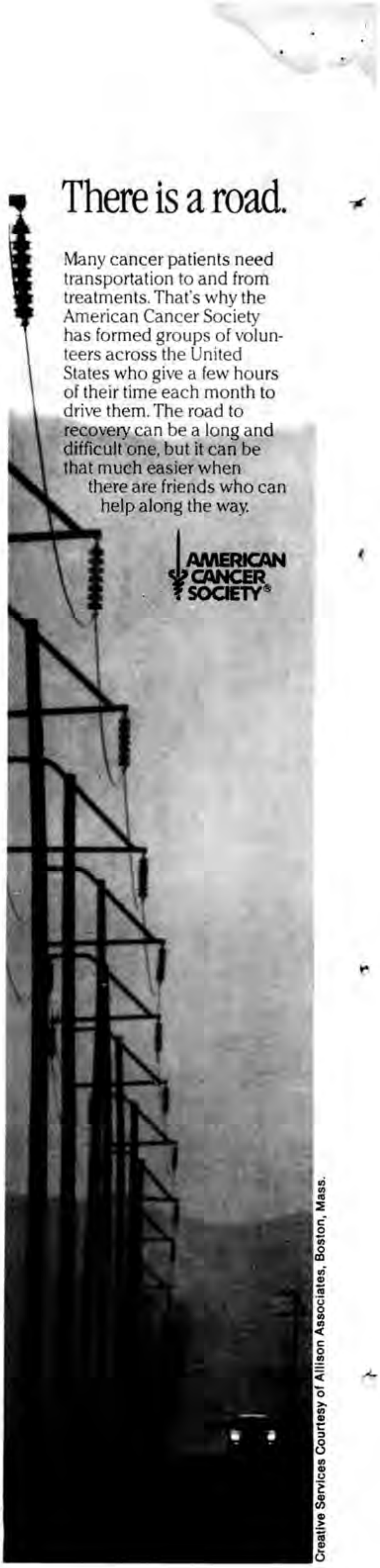

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PRECAUTIONS Impaired Respiration At the usual adult dose of 10mg/70 kg, NUBAIN causes some respiratory depression approximately equal to that produced by equal doses of morphine. However, in contrast to morphine, respiratory depression is not appreciably increased with higher doses of NUBAIN. Respiratory depression induced by NUBAIN can be reversed by NARCAN® (naloxone hydrochloride) when indicated. NUBAIN should be administered with caution at low doses to patients with impaired respiration (e.g., from other medication, uremia, bronchial asthma, severe infection, cyanosis or respiratory obstructions). **Impaired Renal or Hepatic Function** Because NUBAIN is metabolized in the liver and excreted by the kidneys, patients with renal or liver dysfunction may overreact to customary doses. Therefore, in these individuals, NUBAIN should be used with caution and administered in reduced amounts. **Myocardial Infarction** As with all potent analgesics, NUBAIN should be used with caution in patients with myocardial infarction who have nausea or vomiting. **Biliary Tract Surgery** As with all narcotic analgesics, NUBAIN should be used with caution in patients about to undergo surgery of the biliary tract since it may cause spasm of the sphincter of Oddi.

ADVERSE REACTIONS The most frequent adverse reaction in 1066 patients treated with NUBAIN is sedation 381 (36%). Less frequent reactions are sweaty/clammy 99 (9%); nausea/vomiting 68 (6%); dizziness/vertigo 58 (5%); dry mouth 44 (4%); and headache 27 (3%). Other adverse reactions which may occur (reported incidence of 1% or less) are: **CNS Effects** Nervousness, depression, restlessness, crying, euphoria, floating, hostility, unusual dreams, confusion, faintness, hallucinations, dysphoria, feeling of heaviness, numbness, tingling, unreality. The incidence of psychotomimetic effects, such as unreality, depersonalization, delusions, dysphoria and hallucinations has been shown to be less than that which occurs with pentazocine. **Cardiovascular** Hypertension, hypotension, bradycardia, tachycardia. **Gastrointestinal** Cramps, dyspepsia, bitter taste. **Respiration** Depression, dyspnea, asthma. **Dermatological** Itching, burning, urticaria. **Miscellaneous** Speech difficulty, urinary urgency, blurred vision, flushing and warmth. **Patients Dependent on Narcotics** Patients who have been taking narcotics chronically may experience withdrawal symptoms upon the administration of NUBAIN. If unduly troublesome, narcotic withdrawal symptoms can be controlled by the slow intravenous administration of small increments of morphine, until relief occurs. If the previous analgesic was morphine, meperidine, codeine, or other narcotic with similar duration of activity, one-fourth of the anticipated dose of NUBAIN can be administered initially and the patient observed for signs of withdrawal, i.e., abdominal cramps, nausea and vomiting, lacrimation, rhinorrhea, anxiety, restlessness, elevation of temperature or piloerection. If untoward symptoms do not occur, progressively larger doses may be tried at appropriate intervals until the desired level of analgesia is obtained with NUBAIN. **Management of Overdosage** The immediate intravenous administration of NARCAN® (naloxone hydrochloride) is a specific antidote. Oxygen, intravenous fluids, vasopressors and other supportive measures should be used as indicated. The administration of single doses of 72 mg of NUBAIN subcutaneously to eight normal subjects has been reported to have resulted primarily in symptoms of sleepiness and mild dysphoria.

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July 1987
Volume 206, Number 1

Annals of
Surgery

Endoscopy in Colonic Volvulus

THOMAS E. BROTHERS, M.D., WILLIAM E. STRODEL, M.D., F.A.C.S., and FREDERIC E. ECKHAUSER, M.D., F.A.C.S.

From the Department of Surgery, University of Michigan, Ann Arbor, Michigan

Flexible fiberoptic gastrointestinal endoscopy has greatly simplified the diagnosis and treatment of colonic volvulus. The management of 39 patients with colonic volvulus treated over 9 years was reviewed. Five per cent were treated with rectal tube decompression alone, 23% were treated with either sigmoidoscopic or colonoscopic reduction, and 26% were treated exclusively with operation. Endoscopic reduction was attempted in nearly half of the patients in preparation for operation. Recurrent volvulus occurred in 57% of patients initially treated with endoscopic reduction alone. Sigmoidoscopic examination did not confirm the diagnosis in 24% of instances in which it was used, although colonoscopy was always diagnostic. The overall mortality rate was 8%, but increased to 25% in patients with gangrene of the colon. Three patients who later proved to have gangrene of the colon had a normal initial sigmoidoscopic examination. Two of these patients died of intra-abdominal sepsis from a perforated colon. In five patients an accurate endoscopic diagnosis of gangrene prompted immediate exploration. None of these patients died. Endoscopy is a safe and effective diagnostic tool for the initial evaluation of patients with suspected colon volvulus. In addition, endoscopy may result in therapeutic decompression and may provide visual assessment of the viability of the bowel mucosa, thus assisting in the timing of appropriate operative treatment.

VOLVULUS OF THE COLON is a surgical emergency that can lead to significant morbidity and mortality if unrecognized or inadequately treated. Torsion of the bowel on its mesentery occurs most commonly in patients with an excessively mobile colon and may compromise the blood supply to the colon.[1] Factors that may predispose to excessive motility include an elongated mesentery or a mesentery with a narrow base. The most important prognostic factor for the patient with volvulus is the viability of the colon at operation.[2-4]

The management of colonic volvulus depends in part on the site of the volvulus. Successful treatment relies on early recognition and timely intervention. Historically, volvulus has been managed by either transanal rectal tube decompression or by operative intervention. The latter may consist of simple detorsion, tube decompression (cecostomy), fixation of the mobile bowel to the abdominal wall (cecopexy), or resection with primary or delayed anastomosis.[5,6]

The role of endoscopy in the diagnosis and treatment of volvulus has evolved gradually. Operative exploration, as described by Moynihan in the first part of the twentieth century, was considered mandatory when volvulus was proven or even suspected.[7] In 1947, Bruusgaard described rigid sigmoidoscopy as part of the nonoperative management of sigmoid volvulus.[8] When coupled with the placement of a rectal tube, sigmoidos-

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Submitted for publication: December 17, 1986.

copy resulted in a low mortality rate (2–3%), but a high rate of recurrence (40–60%).[9] The development of flexible fiberoptic endoscopy has facilitated decompression of the dilated and friable bowel.[10–12] When used before a definitive operation, the patient's condition can be stabilized, allowing preparation of the bowel for any definitive procedure, including resection and primary anastomosis. In addition, total colonoscopy permits evacuation of bowel contents proximal to the site of the volvulus, and in rare cases has been used to reduce a cecal volvulus. In some institutions colonic endoscopy is used alone as definitive treatment for colon volvulus. This review examines a 9-year experience with endoscopic intervention in colonic volvulus at the University of Michigan.

Methods

The medical records of 39 patients with colonic volvulus treated at the University of Michigan Affiliated Hospitals from October 1, 1975 to October 1, 1984 were reviewed. Patients were categorized according to age and sex, presenting signs and symptoms, and associated medical disorders. The anatomic site of volvulus was identified as full cecal, cecal bascule (cecal fold), transverse colon, splenic flexure, or sigmoid colon. The diagnosis of colonic volvulus was determined by the following modalities, exclusively or in combination: abdominal x-ray, barium enema, history and physical examination, sigmoidoscopy, colonoscopy, operation, or autopsy. Therapeutic procedures included rectal tube decompression, sigmoidoscopy, colonoscopy, laparotomy with either cecopexy, cecostomy, resection and primary anastomosis, or resection and enterostomy. The presence of gangrenous bowel was noted. Instances of recurrent volvulus or of original misdiagnosis were recorded. Patients who had endoscopic decompression followed by planned operation were not considered as having recurrent volvulus.

Results

Thirty-nine patients were identified over a 9-year period at two hospitals: 20 at a university referral center and 19 at a county hospital in a metropolitan area. The average patient age was 59 years. The mean ages for patients with sigmoid and cecal volvulus were 65 years and 50 years, respectively. Fifty-seven per cent of patients were men. Forty-one per cent of patients had had previous abdominal operations, and 13% had had previous episodes of colonic volvulus. Neurologic or psychiatric disorders were present in 36% of patients, and 36% were residents of nursing homes, psychiatric hospitals, or state institutions. Twenty-eight per cent of patients regularly used laxatives.

The most common presenting signs and symptoms were abdominal distention (95%), abdominal pain and cramping (92%), and nausea and vomiting (54%). Less common findings included leukocytosis (white blood count > 10,000/mm^3 in 50%, obstipation (49%), recent constipation (49%), fever (38%), absent bowel sounds (33%), and diarrhea (28%). Only 15% of patients were hemodynamically unstable.

Diagnostic modalities used included plain abdominal x-rays (90%), laparotomy (69%), sigmoidoscopy (54%), barium enema (28%), and colonoscopy (21%). Although not always diagnostic of volvulus, results of all of the above studies except sigmoidoscopy were abnormal. Twenty-four per cent of sigmoidoscopic examinations (18% of all endoscopic procedures) were normal despite the presence of volvulus, yielding a sensitivity of 0.76. False-negative results usually occurred in cases where a more proximal volvulus was present. In no case was the diagnosis of volvulus made solely at autopsy.

The volvulus occurred in the sigmoid colon, cecum, and transverse colon in 56%, 41%, and 5% of patients, respectively. Cecal bascule was diagnosed in one patient (2%).

An average of 1.7 procedures were performed per patient (see Fig. 1). Rectal tube decompression with or without endoscopy was used in 33% of patients. Two patients treated exclusively with rectal tube decompression had no recurrences. Fifty-one per cent of patients had sigmoidoscopic examination, and 15% had a colonoscopic examination. Colonoscopy was successful in five of eight (63%) attempts at reduction of a sigmoid volvulus, and sigmoidoscopy succeeded in 11 of 21 (52%) attempts. In patients in whom endoscopy was the initial therapeutic modality, the recurrence rate was 57%. Laparotomy was performed in 89% of patients. Operations for sigmoid volvulus included resection and primary anastomosis (79%) and resection with colostomy (21%). Cecal volvulus was treated with cecostomy (31%), cecopexy (23%), resection with ileostomy (23%), resection and primary anastomosis (15%), and simple detorsion (8%). Both patients with transverse colon volvulus had colectomy with colostomy. Recurrence after resection and primary anastomosis occurred in one instance of sigmoid volvulus (3%) due to inadequate initial resection. Colon gangrene occurred in 23% of patients. Seventy-seven per cent of these patients were initially examined endoscopically. The overall mortality rate for colonic volvulus was 8%, but increased to 25% in patients with gangrenous changes of the colon. Three patients who later proved to have gangrene of the colon had a normal initial sigmoidoscopic examination. Two of these patients died of intra-abdominal sepsis from a perforated colon. Five patients with necrotic mucosa noted at the time of endoscopy had emergent resection without evidence of perforation. All of these patients survived.

Discussion

The successful treatment of colonic volvulus depends on early recognition of the nature and site of the condition. Although colonic volvulus is not the most common cause of intestinal obstruction (1–6%), it does occur more frequently in institutionalized individuals and in persons over 60 years old.[2,4,13,14] There is speculation that sigmoid volvulus is associated with chronic constipation and high-fiber diets. These factors may result in elongation of the colon and its mesentery, which predisposes it to torsion. In Iran and Russia, where the diet has a high fiber content, there is a high incidence of sigmoid volvulus.[2,8] Indeed, in these two countries, sigmoid volvulus accounts for nearly 50% of all cases of intestinal obstruction. Congenital abnormalities of the colon such as malrotation or inadequate fixation of the cecum have been implicated as the underlying cause of cecal volvulus in younger patients. The average patient age in the current series was 65 years for sigmoid volvulus and 50 years for cecal volvulus. The relative incidence of the various sites of volvulus found in our series is similar to previously published reports (Table 1). Nearly one third of the cases occurred in institutionalized patients, of whom at least 49% had constipation and 28% were chronically taking laxatives.

The presenting signs and symptoms of colon volvulus were the same as any condition that produces intestinal obstruction and include abdominal distention, colic, nausea, vomiting, and obstipation. Signs of systemic toxicity such as fever, leukocytosis, or shock were often absent, even in the presence of bowel gangrene, and were therefore not reliable diagnostic or prognostic indicators in this patient population.

Besides the history and physical examination, the diagnostic study most commonly used was abdominal roentgenography. Barium contrast studies were infrequently used to avoid the possibility of perforation and resultant barium peritonitis. Colonoscopic examination usually confirmed the diagnosis of volvulus. Bloody colonic contents or dark blue or black colonic mucosa were reliable signs of ischemia or impending necrosis. Sigmoidoscopy was frequently unremarkable in cases of colonic volvulus, particularly if the involved segment was proximal to the sigmoid colon. However, a normal colonoscopic examination of the entire colon eliminated the possibility of volvulus. In addition, total colonoscopy would have been useful to identify other causes of colon distention, such as nonobstructive colonic dilatation, or other mechanical factors such as polyps or cancers.[15]

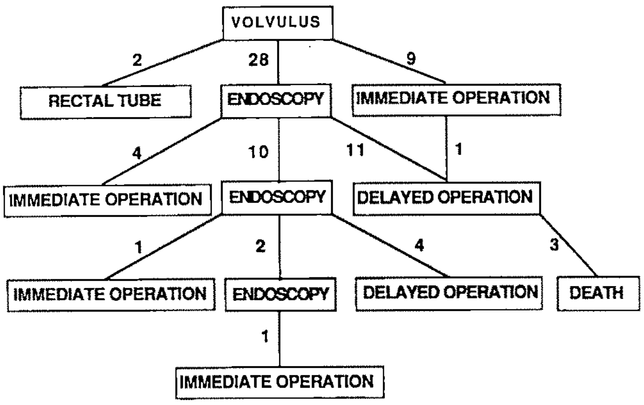

FIG. 1. Treatment progression in 39 patients with colonic volvulus.

Successful colonoscopic reduction of cecal volvulus has been reported sporadically,[12] but was not helpful in our series in either of two attempts. In addition to a high failure rate, attempts at colonoscopic reduction of cecal volvulus may only delay necessary operative intervention and probably should not be considered.

The presence of colonic gangrene as an important prognostic factor has often been demonstrated. In a review of the literature, Ballantyne found that the overall mortality rate of colonic volvulus was 10.6%, but increased to 80% when the colon was necrotic.[16] Reviewing the American experience, the outcome was much more favorable, although the mortality rate was still higher for necrotic than for viable colon (26% *vs.* 11%, respectively).[2] O'Mara et al. reported a 33% mortality rate when gangrenous changes were present compared with an overall mortality rate of 12% when the colon was viable.[6] The overall mortality may also depend on the location of the volvulus. Mortality rates range from 7 to 40% for sigmoid volvulus, 0 to 17% for cecal volvulus, 0 to 75% for transverse colon volvulus, and 0 to 7% for splenic flexure volvulus.[2-6,8,9,14,17] The type of operation may affect the outcome at each particular site, although this has not been proven consistently. Five of our patients had gangrenous colon identified at the initial endoscopic examination. Immediate laparotomy and resection of the necrotic colon were performed with

TABLE 1. *Incidence of Colonic Volvulus by Site*

Type	Current Series (1986), N = 39	Ballantyne et al.[2] (1985), N = 137	Jain and Seth[4] (1968), N = 102
Sigmoid	56%	43%	71%
Full cecal	41%	47%	29%
Transverse	5%	3%	0%
Cecal bascale	2%	5%	—
Splenic flexure	0%	2%	—

no deaths. Two patients who subsequently proved to have gangrene of the colon had unremarkable initial sigmoidoscopic examinations and later died. Perforation with intra-abdominal sepsis developed in both patients before death, possibly resulting from the delay in treatment. A third patient survived despite a similar error.

The dangers of endoscopic examination in cases of suspected colon volvulus include missing a (usually more proximal) segment of necrotic bowel and delaying timely resection of the necrotic segment. Perforation of a compromised segment of bowel may also occur. Such examinations must be performed by experienced endoscopists using minimal air insufflation and manipulation to minimize this possibility.

Flexible colonoscopy is useful as a temporizing measure to allow elective preparation of the patient and the colon, but it should be followed initially by definitive operative intervention. Endoscopic decompression alone, although successful in most patients, is followed by a high recurrence rate. The presence of bloody colonic contents, evidence of strangulation and ischemia, or the presence of signs of peritoneal irritation should indicate the need for termination of the procedure and immediate preparation of the patient for operation. An unremarkable sigmoidoscopic examination does not eliminate the possibility of a more proximal colon volvulus. However, a normal colonscopic examination of the entire colon does eliminate the diagnosis of colon volvulus and suggests the need to search for other causes for colon distention, such as nonobstructive colonic dilatation.

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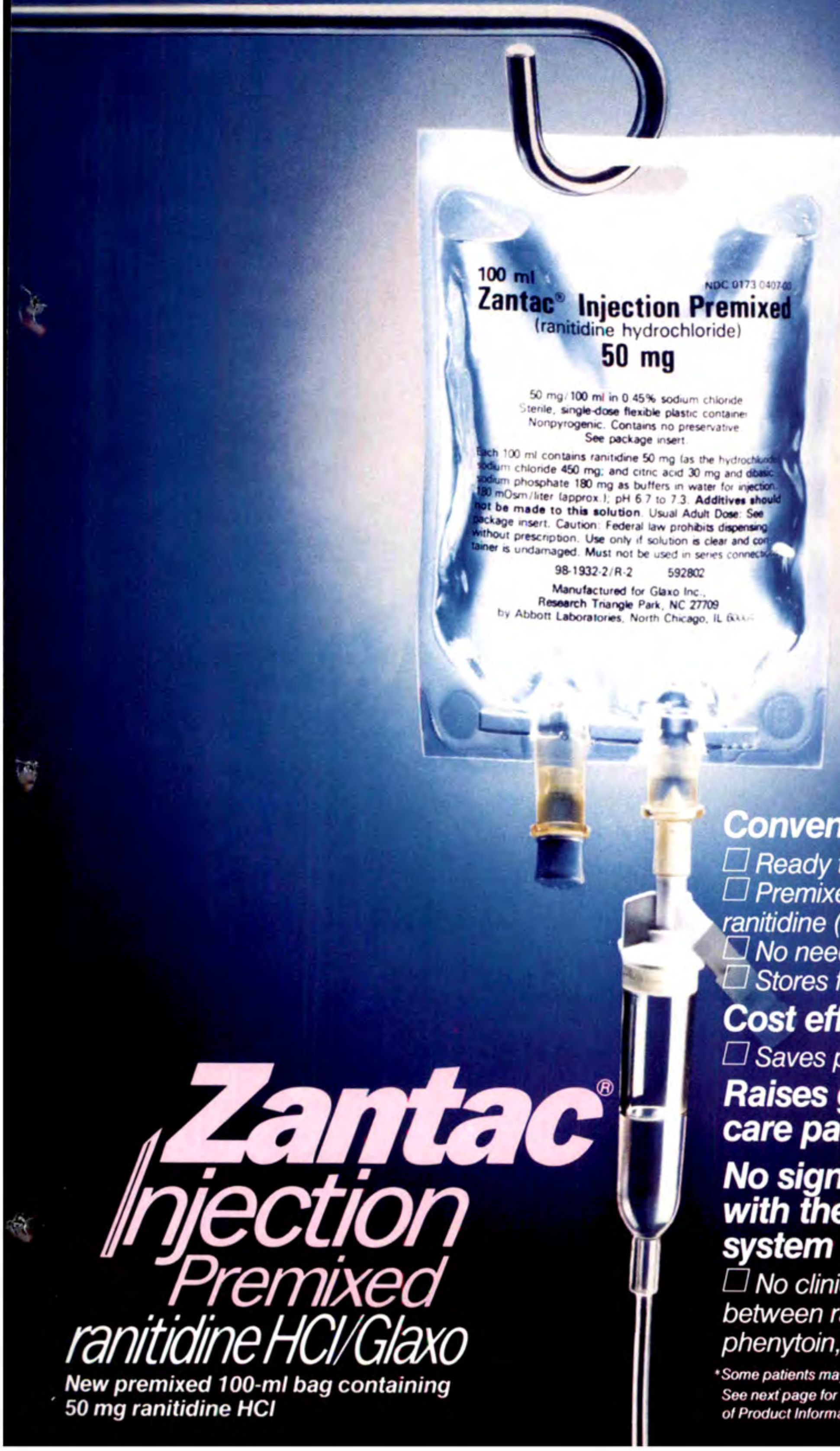
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In normal volunteers, SGPT values were increased to at least twice the pretreatment levels in 6 of 12 subjects receiving 100 mg qid IV for seven days, and in 4 of 24 subjects receiving 50 mg qid for five days. With oral administration there have been occasional reports of reversible hepatitis, hepatocellular or hepatocanalicular or mixed, with or without jaundice.

Reversible blood count changes (leukopenia, granulocytopenia, and thrombocytopenia) have occurred in a few patients. Rare cases of agranulocytosis or of pancytopenia, sometimes with marrow hypoplasia, have been reported.

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(NDC 0173-0362-01) 2-ml single-dose, prefilled, disposable cartridge-needle units (Tray of 10)
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The Role of the Small Intestine in Ammonia Production after Gastric Blood Administration

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It is commonly believed that the digestion of intraluminal blood by colonic bacteria is the primary cause of increased ammonia production after upper gastrointestinal hemorrage. To evaluate the role of the small intestine in ammonia production, blood, amino acids, or water (5 mL/kg) was administered as a meal or enema to awake dogs with chronic indwelling catheters. After blood meals, intestinal ammonia production increased rapidly to peak at 60 minutes and returned to basal levels. This response was mimicked by the gastric administration of ammoniagenic amino acids. No change in ammonia production occurred with water administration. In contrast, colonic blood administration resulted in a gradual rise in ammonia production, and peaked at 150 minutes. Amino acid enemas resulted in a similar but somewhat more rapid response. No change occurred with water enemas. After gut decontamination, ammonia production did not increase after blood enemas. However, the rapid increase in ammonia production persisted after blood meals. It is concluded that both the small bowel and colon participate in the augmented ammonia production that occurs after upper gastrointestinal hemorrhage. Gut decontamination reduces ammonia production by altering the colonic microflora, but is not specific therapy directed towards amino acid metabolism by the enterocytes of the small bowel and thus, does not alter the ammonia produced by the small intestine.

After upper gastrointestinal tract hemorrhage, ammonia concentration in the portal venous blood is elevated.[1,2] The primary site of the increased ammonia production has been believed to be the colon, where bacteria deaminate intraluminal nitrogenous substances. The ammonia produced diffuses into the portal blood stream.[2-5] Other studies have questioned the role of intraluminal bacteria as the primary sources of ammonia generation. For example, Nance et al. administered blood meals to germ-free Eck-fistula dogs and found that the ammonia concentrations in the peripheral blood rose to levels comparable to those observed in animals colonized with bacteria.[6] Rudman and associates administered ammoniagenic amino acids to patients with portosystemic shunting. They observed a rise in ammonia concentration in peripheral blood after intravenous amino acid infusion and concluded that the usual mechanisms of amino acid metabolism were responsible for the augmented ammonia generation.[7]

Other studies have demonstrated that the enterocytes of the small bowel extract glutamine and use this amino acid as a primary oxidizable fuel.[8,9] The ammonia produced is released into the portal blood stream. Estimates suggested that glutamine degradation by the small intestine accounts for approximately half of the ammonia produced by the gastrointestinal tract in the basal state.[10]

The current studies evaluated the role of the small bowel in intestinal ammonia production after a blood meal. These investigations demonstrate that both the small intestine and colon participate in the ammoniageneis that occurs after gastrointestinal bleeding. However, different mechanisms appear to be involved in the processing of intraluminal blood protein.

Materials and Methods

Preparation of Catheterized Dogs

Nineteen conditioned male and female mongrel dogs weighing between 13 and 35 kg (mean: 25 kg) were studied. An average of three studies were performed with each animal. The animals were maintained in accordance with the recommendations of the Committee on

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Animal Care of the Harvard Medical School and Guidelines for the Care and Use of Laboratory Animals (DHSS Publication No. 85-23, Revised 1985). The dogs were acquired from an animal research supplier after they had undergone screening and treatment for parasites. The female dogs were nongravid. All dogs were obtained at least 3 days before operation to allow acclimatization to our facility.

All animals had laparotomy, splenectomy, and placement of chronically indwelling aortic, portal venous, and mesenteric infusion catheters as previously described.[11] After insertion of the catheters into the vessels, the distal ends were exteriorized through a puncture wound in the right flank and needles fitted with injection ports were attached to the catheter tips. The injection ports were placed subcutaneously on the right upper flank of the animal. This allowed chronic access to the blood stream after transcutaneous needle puncture of the injection ports.

The animals were housed individually after operation and received a daily food ration (50 g/kg) of Agway Respond 2000 (Agway, Syracuse, NY) (approximate calorie distribution: no less than 21% protein and 19% fat, with the remaining energy as carbohydrate) between 12:00 A.M. and 4:00 P.M. All animals maintained their preoperative weight or gained weight during a recovery period of at least 1 week. Animals entered into the study met the following criteria: (1) recovered 8 or more days after laparotomy, (2) rectal temperature <39 C, (3) no evidence of infection on physical examination, (4) hematocrit >30%, (5) consumption of all daily food ration with normal stools, (6) normal behavior and energy level, and (7) ability to stand quietly in a Pavlov stand.

Study Design

On the day before the study, the food pan was removed at 4:00 P.M. All studies were performed between 7:00 A.M. and 2:00 P.M. in animals fasted more than 15 hours. On the morning of the study, the dogs were exercised and then placed in a Pavlov stand. Rectal temperature was taken, and the catheter injection ports entered by percutaneous puncture with 21-gauge needles. All catheters were flushed with heparinized saline (2 units of heparin/mL 0.9% saline).

Infusion of a solution of para-aminohippurate sodium (PAH, Merck, Sharp, and Dome, West Point, PA) in 0.9% saline (0.5 g PAH/100 mL 0.9% saline) was begun *via* the mesenteric infusion catheter. After an initial priming dose, the solution was infused at a rate of 0.70 mL/min *via* a Harvard pump (Harvard Equipment Co., South Natick, MA). After at least 45 minutes of infusion, steady-state dye concentrations were achieved and basal blood samples were obtained.[12] Six basal sample pairs were drawn simultaneously from the aortic and portal venous catheters for determination of whole blood ammonia, glutamine, glutamate, and PAH. The first three pairs were drawn at 5-minute intervals, and after 10 minutes, the second three pairs were drawn in a similar manner.

The animals then received either a meal or enema composed of one of the following: blood, an amino acid solution, or water. All meals or enemas were administered in a volume of 5 mL/kg. Meals were administered *via* an orogastric tube inserted through a wooden bite block with a hole in its center, which was placed in the dog's mouth. The tube and bite block were removed immediately after meal administration. Enemas were administered slowly *via* a Foley catheter that was advanced maximally (35 cm) into the animal's descending colon. After enema administration the tube was clamped and the catheter was pulled back until the Foley balloon was just proximal to the anal sphincter. The Foley balloon was then inflated with 20 mL of tap water and allowed to rest in the rectal vault for the remainder of the study period. The rectal tube was well tolerated by the animals, and its presence facilitated retention of the enemas.

Samples for whole blood ammonia and PAH were drawn simultaneously and in triplicate from the aortic and portal venous catheters at 30, 60, 90, 150, and 210 minutes after meal or enema administration. Triplicate samples for whole blood glutamine and glutamate were similarly drawn at 30, 90, and 210 minutes. At each time point three sample pairs were drawn: one pair was drawn 5 minutes before the time, the second was drawn at the specific time, and the third pair was drawn 5 minutes after the time point. Glutamine and glutamate determinations were not performed after the administration of the amino acid solutions.

Blood aliquots for ammonia, glutamine, and glutamate were immediately deproteinized with 10% perchloric acid placed in ice, periodically centrifuged, and filtered. The filtrates were pH adjusted and stored at −20 C until analysis by an enzymatic assay.[13] PAH samples were deproteinized with 10% trichloroacetic acid, filtered, and stored at −20 C until measurement by a spectrophotometric technique.[14] Whole blood ammonia determinations were performed using a spectrophotometric enzymatic assay (Sigma Chemical Co., St. Louis, MO).

Preparation of Blood and Amino Acid Meals and Enemas

Blood for meals or enemas was harvested from a donor dog less than 24 hours before each study. The average quantity harvested was approximately 200 mL. Blood was withdrawn, heparinized (1000 units), and refrigerated until 1 hour before the study. During this time the blood was warmed in room temperature until administered. Aliquots from each donor sample were taken for analysis of whole blood nitrogen[15] and ammonia concentration.

The amino acid solutions were prepared from the following four ammoniagenic amino acids[7]: glutamine (gln), serine (ser), threonine (thr) (Sigma Chemical Co., St. Louis, MO), and glycine (gly) (Fisher Scientific, Fair Lawn, NJ). The amino acids were weighed to provide a final concentration of gln 0.028 M, ser 0.12 M, thr 0.091 M, and gly 0.19 M, which approximated their concentrations in whole blood as free amino acids and as constituents of blood proteins.[16] The amino acids were mixed in tap water and administered within 10 minutes to minimize hydrolysis. A sample of each solution was taken for ammonia determination before administration. Tap water alone was also given by meal or enema and served as a control study. All meals or enemas were followed by a 50-mL tap water flush.

Gut Decontamination and Quantitative Stool Cultures

Six chronically catheterized dogs had gut decontamination as previously described.[17] At least 7 days after catheter insertion, antibiotic therapy was initiated. Animals received neomycin sulfate, 50 mg/kg, cephalothin sodium, 50 mg/kg, natamycin, 8 mg/kg, and polymyxin B, 10 mg/kg, twice daily for 7–8 days. The antibiotics were mixed in 100 mL of tap water and administered *via* an orogastric tube. The animals received their last dose of antibiotics the afternoon before the study and were fasted overnight. Each animal was studied twice and received a blood meal and a blood enema on the 5th or 7th–8th day of antibiotic treatment. The order in which the studies were performed (blood meal or enema) was sequentially alternated. The studies were performed after the previously described protocol.

Quantitative stool cultures were performed on each animal before the initiation of antibiotic therapy and after gut decontamination on the morning of blood meal and enema administration. Stool was harvested from the rectal vault using sterile technique and placed in a sterile container. A weighed sample (0.5 g) was suspended in 5 mL of sterile 0.9% saline and thoroughly homogenized. Seven serial dilutions were prepared ranging from 0.1 to 0.6×10^{-11} g stool/mL. One-milliliter aliquots of each dilution were plated in quadruplicate on blood agar plates (Gibco Laboratories, Lawrence, MA). All plates were incubated at 35 C for 48 hours. Two plates from each dilution were incubated in room air, and the other two were placed in a Gaspack Anaerobic jar (Microbiology Systems, Cockeysville, MD). After 48 hours, the plates were inspected for growth. Only the plates with discreet colonies were counted. The counts of duplicate plates were averaged to determine the number of colony-forming units per milliliter of aliquot plated. This number was then corrected by the dilution factor to calculate the number of colony-forming units per gram of stool. For each study, the final number of aerobes and anaerobes represents the average of all the dilutions where colonies could be counted (usually 2–3 plates).

Calculations

Portal blood flow was calculated using the dye dilution technique as previously described[12] and expressed per kilogram of body weight. For each study and substrate, the basal value for the arterial and portal venous concentration, portal venous–arterial (PV-A) concentration difference, and portal blood flow was calculated as the mean of the six basal measurements. Substrate exchange for each point in time was calculated as the mean of the product of portal blood flow and PV-A concentration difference; the six basal exchange rates were averaged for each substance to calculate basal substrate exchange, whereas the triplicate exchange rates were averaged for the specific time point after a meal or an enema. The values at each point in time from all studies within a treatment group were meaned.

For each individual experiment, the basal–peak response for each parameter was calculated by subtraction of the basal from the maximal value after a meal or enema. The time of peak response was determined by inspection of each individual response curve. Total ammonia production was calculated by integrating the area above basal subtended by each ammonia production curve. For each treatment group, these calculations were averaged to determine the mean basal–peak response, average time of peak response, and mean total ammonia production.

Statistical Analysis

The data were tested for distribution and found to be normally distributed; parametric methods were used to make all comparisons. Basal PV-A concentration differences were t-tested to determine if they were different than zero. Correlation was used to compare the arterial and portal concentrations of each substrate in the basal state. Within a treatment group, substrate concentrations, PV-A concentration differences, portal blood flow, and substrate exchange at each time point were compared with basal values (T = 0) using Dunnett's test in a blocked manner.[18] Regression analysis was used to determine the relationship between a specific measurement and time. Basal-to-peak response, time of peak response, and total ammonia production were com-

TABLE 1. *Average Values for Substrate Concentration, Blood Flow, and Gastrointestinal Exchange Measured in the Basal State (Mean ± SEM)**

	Portal Concentration (μmol/L)	Arterial Concentration (μmol/L)	Portal-Arterial Difference (μmol/L)	Portal Blood Flow (mL/min/kg)	Gastrointestinal Exchange	
					Measured Flow (μmol/min/kg)	Assumed Flow (μmol/min/kg)
Ammonia	349 ± 13 (52)	174 ± 8 (52)	175 ± 10† (52)	28 ± 2 (33)	5.39 ± 0.42 (33)	4.83 ± 0.33 (52)
Glutamine	676 ± 16 (31)	748 ± 18 (31)	−73 ± 7† (31)	28 ± 2 (33)	−1.70 ± 0.24 (19)	−1.87 ± 0.20 (19)
Glutamate	74 ± 3 (31)	67 ± 3 (31)	7 ± 1† (31)	28 ± 2 (33)	0.21 ± 0.03 (19)	0.19 ± 0.02 (19)

* Number of studies in parentheses.

† $p < 0.01$ when compared with 0.

(−) designates uptake, (+) designates release.

pared between groups by unpaired t-test. Paired t-test was used to compare blood meals and blood enemas after gut decontamination as the same studies were done in each animal.

Dunnett's test was performed on a Hewlett Packard 9845 microcomputer (Hewlett Packard, Palo Alto, CA) using the statistical software package Analyzer (1985 version by Dr. B. J. Ransil, Department of Medicine, Beth Israel Hospital, Boston, MA). All other calculations were performed using the Harvard School of Public Health computer (Boston, MA) using the Minitab statistical software package (Ed Magnin, 1983, Pennsylvania State University, University Park, PA). All data are expressed as mean ± SEM.

Results

Basal Studies

The overnight preparation of the animals was the same in 52 studies performed in 17 animals; these data form the basis for the basal measurements (Table 1). The mean portal ammonia concentration was 349 ± 13 μmol/L, almost twice the concentration found in arterial blood. Both of these levels were similar to previous reports from this laboratory[8] and elsewhere.[6] Basal portal glutamine concentration was 676 ± 16 μmol/L, approximately 10% lower than the mean arterial concentration and similar to previous reports.[11] In contrast, portal glutamate levels were approximately 10% higher than arterial levels. All the PV-A concentration differences were significantly different from zero, indicating that the gastrointestinal tract extracted or released the substances measured.

Mean basal portal blood flow measured in 33 studies was 28 ± 2 mL/min/kg, similar to values previously reported in splenectomized animals.[11] Gastrointestinal exchange of ammonia, glutamine, and glutamate were similar to rates previously reported.[8] In studies in which flow was not measured, the average basal portal blood flow was used to calculate substrate exchange in these animals. When both measured and derived exchange rates were averaged, the combined results for the 52 studies were similar to the rates measured in the 33 studies (Table 1).

In all studies, arterial and portal concentration were generally related; the correlation (r^2) between arterial and portal venous ammonia concentrations was 0.44, for arterial and portal glutamine levels was 0.92, and for arterial and portal glutamate concentrations was 0.85 ($p < 0.05$ for all relationships). There was, however, no significant relationship between the arterial and portal venous concentrations of these substances and their respective rates of gastrointestinal exchange, suggesting that other factors participate in the maintenance of these blood levels.

Effect of Blood and Water Meals

The effect of blood administered by orogastric tube on intestinal substrate flux was studied in eight animals. After blood administration, there was a prompt rise in portal venous ammonia, glutamine, and glutamate concentrations (Tables 2 and 3). These levels remained elevated for up to 90 minutes, then returned to normal basal concentrations. During this time there was a slight but significant increase in the arterial concentrations of glutamine and glutamate. The increases in portal concentration were reflected by significant widening of the PV-A gradient for ammonia and a narrowing of the gradient for glutamine. Portal blood flow remained constant after blood meals. Gastrointestinal production of ammonia increased significantly between 30 and 90 minutes compared with basal release rates. Glutamine extraction decreased significantly at 30 minutes, whereas glutamate production increased significantly at 90 minutes.

The effect of water meals was studied in seven animals. After administration of water in volumes equal to that of blood, there was no significant change in concentrations of ammonia, glutamine, or glutamate in the

TABLE 2. *Ammonia Concentrations, Blood Flow, and Gastrointestinal Ammonia Production After Blood and Water Meals (Mean ± SEM)*

Time in Minutes	0	30	60	90	150	210
Blood meals (N = 8)						
Portal venous (μmol/L)	311 ± 66	459 ± 72*	480 ± 27*	481 ± 51*	377 ± 29	360 ± 35
Arterial (μmol/L)	167 ± 23	210 ± 18	210 ± 30	207 ± 36	194 ± 17	186 ± 20
PV-A (μmol/L)	145 ± 17	251 ± 29*	270 ± 35*	274 ± 35*	182 ± 23	173 ± 24
Portal blood flow (N = 3) (ml/min/kg)	24 ± 4	25 ± 7	24 ± 4	25 ± 5	22 ± 8	26 ± 7
Ammonia production (μmol/min/kg)	3.89 ± 0.51	6.54 ± 0.72*	6.97 ± 0.73*	6.69 ± 0.91*	4.65 ± 0.74	4.65 ± 0.74
Water meals (N = 7)						
Portal venous (μmol/L)	340 ± 147	345 ± 57	345 ± 53	319 ± 47	338 ± 40	319 ± 39
Arterial (μmol/L)	187 ± 26	193 ± 36	190 ± 26	190 ± 25	188 ± 25	176 ± 23
PV-A (μmol/L)	150 ± 33	151 ± 42	155 ± 43	128 ± 35	150 ± 29	143 ± 23
Portal blood flow (N = 2)	27 ± 5	29 ± 1	30 ± 2	31 ± 1	35 ± 2	32 ± 3
Ammonia production (μmol/min/kg)	4.29 ± 0.93	4.24 ± 1.17	4.39 ± 1.21	3.75 ± 0.99	4.54 ± 0.82	4.27 ± 0.62

* $p < 0.01$ when compared with T = 0 by Dunnett's test.

portal vein (Tables 2 and 3). However, arterial glutamine concentration rose gradually with time ($r^2 = 0.89$, $p < 0.05$), to a level significantly greater than the initial basal concentration. No significant alteration of arterial ammonia or glutamate concentration occurred. The PV-A gradient for each substrate remained constant as did portal blood flow; hence exchange rates for each substrate were constant throughout the study period.

When the basal-to-peak concentration differences after blood and water meals were compared, the rises in the portal concentration of ammonia, glutamine, and glutamate were significantly different from the water meal (Table 4). Similarly, the basal-to-peak response for ammonia production was greater after blood administration, as was the total quantity of ammonia produced (Table 4, Fig. 1).

Effect of Blood and Water Enemas

The effect of blood administered by rectal catheter was studied in eight animals. After colonic blood administration, there was a gradual rise with time in portal ammonia ($r^2 = 0.93$, $p < 0.01$), ammonia PV-A difference ($r^2 = 0.98$, $p < 0.001$), and in intestinal ammonia production ($r^2 = 0.74$, $p < 0.05$, Fig. 2). These levels were significantly greater than initial basal values at 150

TABLE 3. *Portal, Arterial, PV-A Difference and Exchange of GLN and GLU After Blood or Water Meals (Mean ± SEM)*

Time in Minutes	0	30	90	210
Blood meals (N = 8)				
Portal vein (μmol/L)				
GLN	663 ± 20	853 ± 30†	788 ± 40†	747 ± 41†
GLU	74 ± 4	80 ± 4†	95 ± 4*	93 ± 3
Arterial (μmol/L)				
GLN	756 ± 13	877 ± 16†	849 ± 35†	823 ± 41
GLU	73 ± 4	81 ± 4*	78 ± 4	74 ± 4
PV-A (μmol/L)				
GLN	−93 ± 11	−39 ± 13*	−61 ± 18	−75 ± 11
GLU	6 ± 1	15 ± 4	16 ± 3	6 ± 2
Gastrointestinal exchange (μmol/min/kg)				
GLN	−2.45 ± 0.30	−0.74 ± 0.64*	−1.50 ± 0.56	−2.02 ± 0.33
GLU	0.16 ± 0.04	0.33 ± 0.06	0.58 ± 0.17*	0.18 ± 0.06
Water meals (N = 8)				
Portal vein (μmol/L)				
GLN	681 ± 27	698 ± 28	726 ± 33	733 ± 46
GLU	73 ± 4	73 ± 4	71 ± 6	70 ± 6
Arterial (μmol/L)				
GLN	739 ± 35	750 ± 38	789 ± 45	812 ± 46†
GLU	67 ± 4	66 ± 4	65 ± 5	64 ± 5
PV-A (μmol/L)				
GLN	−58 ± 22	−51 ± 18	−62 ± 18	−79 ± 12
GLU	6 ± 1	8 ± 1	5 ± 1	7 ± 1
Gastrointestinal exchange (μmol/min/kg)				
GLN	−1.45 ± 0.57	−1.44 ± 0.50	−1.90 ± 0.48	−2.28 ± .031
GLU	0.16 ± 0.03	0.21 ± 0.03	0.16 ± 0.03	0.19 ± 0.04

* $p < 0.05$, †$p < 0.01$ when compared with T = 0 by Dunnett's test.

TABLE 4. *Comparison of the Effects of Blood or Water Meals on Ammonia, Glutamine, and Glutamate*

Basal–Peak Responses	Blood Meals	Water Meals
Portal vein ammonia (μmol/L)	229 ± 24	31 ± 16†
Portal vein glutamine (μmol/L)	199 ± 26	72 ± 25*
Portal vein glutamate (μmol/L)	20 ± 4	2 ± 3*
Gastrointestinal ammonia production (μmol/min/kg)	3.55 ± 0.54	0.83 ± 0.54*
Integrated area for ammonia (μmol/kg)	377 ± 77	0 ± 66*

* $p < 0.01$, † $p < 0.001$ by unpaired t-test.

and 210 minutes (Table 5). No significant change was observed in arterial ammonia concentration. Portal blood flow remained constant throughout the study period. No significant changes occurred in the portal concentrations of glutamine or glutamate, nor in their respective PV-A concentration differences or rates of gastrointestinal exchange (Table 6).

The effect of a water enema was studied in eight animals. When water was administered in volumes equal to that of blood, no significant changes occurred (Tables 5 and 6). Sham enemas were performed in five additional animals. This involved rectal catheterization without volume administration; no significant changes from basal occurred in the substrate concentrations after this manipulation (data not shown).

Comparison of Route of Blood Administration

Basal-to-peak responses between blood meals and enemas were compared to determine the effect of the route of blood administration (Table 7). Responses for portal ammonia, PV-A concentration difference, and intestinal ammonia production were similar. However, for all these measurements, the time of peak response was significantly delayed after colonic blood administration. The peak responses for blood meals occurred at 60 ± 30 minutes, compared with the peak response time of 150 ± 30 minutes after blood enemas. Total ammonia production was similar in each group. The average quantity of ammonia present in the blood administered as meals and enemas was 1.57 μmol/kg, and the ammonia produced was 99% greater than this quantity. The average quantity of whole blood nitrogen administered in the blood meals and enemas was 11 mmol/kg, and only 3.6% of the total nitrogen administered was recovered as ammonia after meal or enema administration.

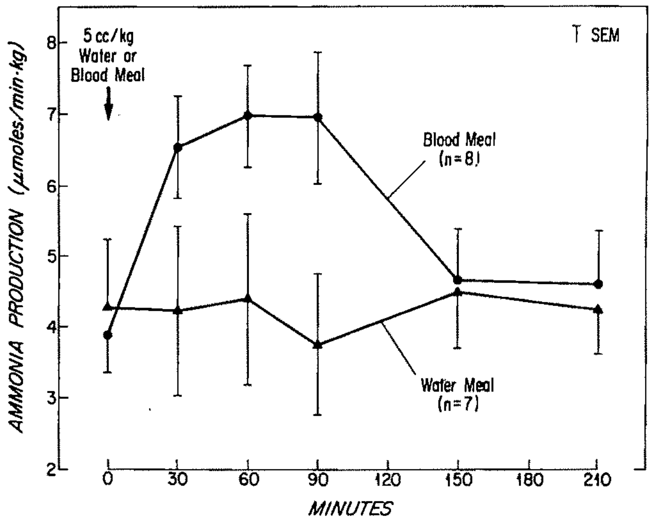

FIG. 1. After gastric intubation and blood administration, gastrointestinal ammonia production greatly increased between 30 and 90 minutes, then returned to basal levels. Ammonia production did not change after water administration.

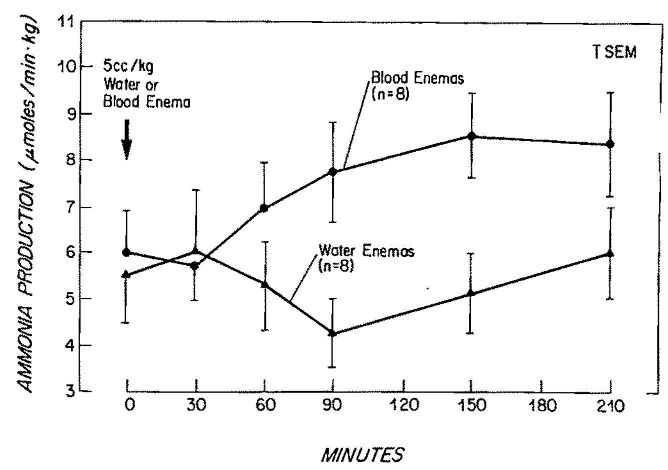

FIG. 2. After instillation of blood into the colon, ammonia production rose gradually and was still elevated by 210 minutes. Ammonia production did not change after water enemas.

The mean peak response for arterial ammonia was significantly greater after meals than after enemas. No difference in the time of peak response of arterial ammonia was observed.

Effect of Amino Acid Meals and Enemas

To evaluate the effect of digested protein on ammonia produced by the gastrointestinal tract, amino acids were administered by meal or enema. After amino acid meals, a rapid, significant rise occurred in the arterial and portal concentrations of ammonia at 30 minutes, with both concentrations returning to basal values by 60 minutes (Table 8). Portal blood flow remained constant after amino acid meals. Gastrointestinal ammonia production increased significantly at 30 minutes and returned to basal value by 60 minutes.

The effect of the same amino acid solution adminis-

TABLE 5. *Ammonia Concentrations, Blood Flow, and Gastrointestinal Ammonia Production After Blood or Water Enemas (Mean ± SEM)*

Time in Minutes	0	30	60	90	150	210
Blood enemas (N = 8)						
Portal venous (μmol/L)	362 ± 34	352 ± 47	419 ± 34	442 ± 38	480 ± 52*	527 ± 83†
Arterial (μmol/L)	156 ± 25	136 ± 20	172 ± 25	181 ± 23	165 ± 33	146 ± 22
PV-A (μmol/L)	206 ± 20	216 ± 30	247 ± 26	261 ± 28	314 ± 35*	381 ± 71†
Portal blood flow (N = 7) (mL/min/kg)	32 ± 5	33 ± 7	31 ± 5	31 ± 5	31 ± 5	26 ± 6
Ammonia production (μmol/min/kg)	5.99 ± 0.91	5.80 ± 0.87	7.07 ± 0.85	7.83 ± 1.11	8.50 ± 0.90†	8.26 ± 1.07*
Water enemas (N = 8)						
Portal venous (μmol)	404 ± 35	437 ± 57	456 ± 32	484 ± 55	474 ± 50	463 ± 70
Arterial (μmol/L)	200 ± 20	222 ± 24	235 ± 17	302 ± 50	268 ± 20	293 ± 50
PV-A (μmol/L)	204 ± 28	215 ± 42	221 ± 29	182 ± 26	205 ± 36	195 ± 30
Portal blood flow (N = 7) (mL/min/kg)	24 ± 7	26 ± 3	22 ± 2	22 ± 3	25 ± 5	26 ± 4
Ammonia production (μmol/min/kg)	5.57 ± 1.12	5.96 ± 1.42	5.27 ± 0.79	4.22 ± 0.65	5.08 ± 0.92	5.93 ± 0.91

* $p < 0.05$, †$p < 0.01$ when compared with T = 0 by Dunnett's test.

tered by a rectal catheter on the intestinal flux of ammonia was studied in eight animals. After the administration of amino acid enemas in volumes equal to those of meals, portal ammonia concentration increased significantly by 60 minutes and remained elevated over basal concentrations for the remainder of the study period (Table 8). This elevation in portal ammonia concentration was reflected by significant widening of the PV-A concentration gradient over the basal value during the same time period. A transient but significant elevation in arterial ammonia occurred at 90 minutes. Portal blood flow remained constant after amino acid enemas. Gastrointestinal ammonia production increased significantly from 60 to 150 minutes compared with basal release rates.

The basal-to-peak responses for portal and arterial ammonia concentration as well as intestinal ammonia production were similar in the animals given amino acid meals or enemas (Table 9). However, the basal-to-peak ammonia PV-A concentration difference was significantly greater after colonic instillation of amino acids compared with gastric administration. For all responses, the time of peak response over basal was significantly delayed after enemas compared with after meals. Although amino acid enemas tended to produce more total ammonia for the study period compared with

TABLE 6. *Portal, Arterial, PV-A Difference and Exchange of GLN and GLU After Blood or Water Enemas (Mean ± SEM)*

Time in Minutes	0	30	90	210
Blood enemas (N = 8)				
Portal vein (μmol/L)				
GLN	692 ± 33	717 ± 35	733 ± 42	752 ± 52
GLU	77 ± 7	70 ± 8	73 ± 7	71 ± 6
Arterial (μmol/L)				
GLN	758 ± 32	774 ± 37	800 ± 33	821 ± 47*
GLU	70 ± 7	64 ± 9	64 ± 8	63 ± 8
PV-A (μmol/L)				
GLN	−68 ± 9	−58 ± 4	−67 ± 11	−71 ± 14
GLU	8.0 ± 0.8	6.0 ± 1.3	9.0 ± 1.1	8.7 ± 2.0
Gastrointestinal exchange (μmol/min/kg)				
GLN	−2.13 ± 0.37	−1.59 ± 0.28	−2.18 ± 0.42	−2.04 ± 0.53
GLU	0.25 ± 0.04	0.22 ± 0.05	0.33 ± 0.06	0.26 ± 0.10
Water enemas (N = 6)				
Portal vein (μmol/L)				
GLN	669 ± 33	643 ± 58	654 ± 60	711 ± 63
GLU	66 ± 3	66 ± 4	68 ± 5	72 ± 5
Arterial (μmol/L)				
GLN	738 ± 56	738 ± 64	741 ± 67	792 ± 76
GLU	59 ± 3	56 ± 4	59 ± 3	63 ± 3
PV-A (μmol/L)				
GLN	−70 ± 13	−95 ± 16	−86 ± 10	−80 ± 27
GLU	7.8 ± 1.0	10.0 ± 1.0	8.4 ± 2.5	9.9 ± 1.5
Gastrointestinal exchange (μmol/min/kg)				
GLN	−1.40 ± 0.25	−2.13 ± 0.19	−1.86 ± 0.16	−1.51 ± 0.49
GLU	0.20 ± 0.06	0.27 ± 0.06	0.22 ± 0.08	0.24 ± 0.02

* $p < 0.05$ when compared with T = 0 by Dunnett's test.

TABLE 7. *Comparison of the Effects of Blood Meals or Enemas on Ammonia (Mean ± SEM)*

Basal–Peak Responses	Meals	Enemas
Portal ammonia (μmol/L)	229 ± 24	190 ± 62
Arterial ammonia (μmol/L)	86 ± 18*	39 ± 10
PV-A difference (μmol/L)	144 ± 25	153 ± 63
Gastrointestinal ammonia production (μmol/min/kg)	3.55 ± 0.54	3.13 ± 0.77
Time of Peak Response over Basal (Minutes)		
Portal ammonia	60 ± 30	150 ± 30†
Arterial ammonia	90 ± 30	90 ± 30
PV-A difference	60 ± 30	150 ± 30†
Ammonia production	60 ± 30	150 ± 30†
Integrated area (μmol/kg)	377 ± 77	306 ± 147

* $p < 0.05$, †$p < 0.01$ by unpaired t-test.

meals, no significant difference between the integrated areas was detected.

The average quantity of ammonia administered in the amino acid meals and enemas was ≤0.59 μmol/kg, and in each case accounted for ≤6.0% of the total ammonia produced. The average nitrogen dose administered in the amino acid solution was 2.2 mmol/kg. For amino acid meals, 9.4 ± 2.9% of this quantity was recovered as ammonia nitrogen. For enemas, 20 ± 5.0% of the nitrogen was recovered as ammonia.

Effects of Gut Decontamination on Ammonia Production

Initial stool cultures demonstrated a significantly greater number of anaerobic colonies compared with aerobic colonies (Table 10), which is consistent with previous reports.[19] After 5 days or 7–8 days of antibiotic therapy, all colony counts were significantly reduced; there were no significant differences between the number of aerobes or anaerobes. Each postdecontamination colony count represented at least a 93% reduction in colony-forming units per gram of stool when compared with controls.

The mean portal ammonia concentration was 306 ± 15 μmol/L, significantly reduced from the basal concentration in the nonantibiotic-treated animals (Table 11). The arterial ammonia concentration was not significantly altered by antibiotic therapy. The diminished portal ammonia concentration resulted in a significant narrowing of the ammonia PV-A concentration gradient compared with nonantibiotic-treated animals. No alteration occurred in arterial or portal glutamine concentration nor in the PV-A concentration difference. However, both arterial and portal glutamate concentrations were significantly lower than in nonantibiotic-treated animals, but the PV-A concentration gradient was unaltered. All the PV-A concentration differences were significantly different from zero as the gastrointestinal tract continued to extract or release these substrates.

Mean basal portal blood flow measured in six studies was 36 ± 5 mL/min/kg, which is within the range of measurements in nonantibiotic-treated animals (NS when compared with nonantibiotic-treated animals). For glutamine and glutamate, exchange rates were comparable to those in nonantibiotic-treated animals. In contrast, basal gastrointestinal ammonia production was significantly reduced in the decontaminated dogs compared with the nonantibiotic-treated animals.

After the administration of blood by orogastric tube, a rapid rise in portal ammonia concentration occurred by 30 minutes and remained significantly elevated over the initial basal concentration for up to 150 minutes (Table 12). The ammonia PV-A concentration difference widened significantly at 60 and 90 minutes, whereas a transient increase in arterial ammonia concentration occurred at 150 minutes. Portal blood flow remained constant throughout the study period. Intestinal ammonia production increased significantly at 30 minutes and

TABLE 8. *Ammonia Concentrations, Blood Flow, and Gastrointestinal Ammonia Production After Amino Acid Meals or Enemas (Mean ± SEM)*

Time in Minutes	0	30	60	90	150	210
Amino acid meals (N = 8)						
Portal vein (μmol/L)	337 ± 35	483 ± 36†	381 ± 31	359 ± 27	327 ± 26	340 ± 26
Arterial (μmol/L)	155 ± 10	234 ± 19†	176 ± 12	172 ± 16	177 ± 23	175 ± 15
PV-A (μmol/L)	181 ± 27	254 ± 20†	208 ± 24	187 ± 17	150 ± 12	164 ± 17
Portal blood flow (N = 7)	24 ± 4	33 ± 4	31 ± 5	27 ± 8	28 ± 6	28 ± 4
Ammonia production (μmol/min/kg)	4.21 ± 0.58	8.70 ± 1.40†	5.93 ± 0.69	5.18 ± 1.44	3.65 ± 0.59	4.61 ± 0.59
Amino acid enemas (N = 8)						
Portal vein (μmol/L)	356 ± 23	488 ± 47	527 ± 43†	582 ± 73†	559 ± 59†	504 ± 48*
Arterial (μmol/L)	168 ± 14	208 ± 28	202 ± 18	239 ± 29*	199 ± 25	198 ± 21
PV-A (μmol/L)	188 ± 16	279 ± 32	324 ± 33†	342 ± 53†	360 ± 49†	306 ± 45*
Portal blood flow (N = 5)	29 ± 7	23 ± 3	26 ± 5	23 ± 4	24 ± 4	23 ± 5
Ammonia production (μmol/min/kg)	5.26 ± 0.83	6.41 ± 0.93	8.12 ± 0.50*	8.48 ± 1.38*	8.16 ± 1.27*	7.20 ± 1.62

* $p < 0.05$, †$p < 0.01$ when compared with T = 0 by Dunnett's test.

TABLE 9. *Comparison of the Effects of Amino Acid Meals or Enemas on Ammonia (Mean ± SEM)*

Basal–Peak Responses	Meals	Enemas
Portal ammonia (μmol/L)	165 ± 30	293 ± 60
Arterial ammonia (μmol/L)	88 ± 18	93 ± 26
PV-A Difference (μmol/L)	85 ± 17	221 ± 39*
Gastrointestinal ammonia production (μmol/min/kg)	4.71 ± 1.08	4.64 ± 1.[illegible]9
Time of Peak Response over Basal (Minutes)		
Portal ammonia	30 ± 30	90 ± 30†
Arterial ammonia	30 ± 30	90 ± 30‡
PV-A difference	30 ± 30	90 ± 30†
Gastrointestinal ammonia production	30 ± 30	90 ± 30†
Integrated area (μmol/kg)	234 ± 72	468 ± 1[illegible]0

* $p < 0.05$, †$p < 0.01$, ‡$p < 0.001$ by unpaired t-test.

again at 90 minutes. In contrast to the nonantibiotic-treated dogs who received blood meals, no significant changes occurred in the arterial or portal concentrations of glutamine or glutamate, nor in their PV-A concentration gradients or rates of gastrointestinal exchange (Table 13).

After the administration of blood by rectal catheter, portal vein ammonia concentration and PV-A concentration difference did not change significantly from basal measurements, nor did either value increase with time (Table 12). A transient but significant elevation in arterial ammonia occurred at 60 minutes. Portal blood flow remained constant throughout the study period. Intestinal ammonia production remained constant and did not change significantly with time. Portal vein glutamine and glutamate did not change significantly from basal values, nor was there a change in the PV-A concentration gradients (Table 13). Gastrointestinal exchange of these substrates remained constant. Arterial glutamine concentration decreased significantly from initial basal concentrations at 90 and 210 minutes. No change occurred in arterial glutamate concentration.

The basal-to-peak response for portal ammonia concentration, PV-A concentration difference, and gastrointestinal ammonia production were significantly greater after blood meals compared with blood enemas after gut decontamination. No significant difference was observed in the basal-to-peak response for arterial ammonia concentration (Table 14). A significantly greater total quantity of ammonia was produced after meals than after enemas. No significant differences were observed in the time of the peak responses between the two groups.

The ammonia production curves after blood meals were similar with or without gut decontamination (Fig. 3). Both responses were characterized by early elevations in gastrointestinal ammonia production compared with the flat curve observed after water meals. Each trapezoidal curve returned to a value not significantly different from its respective basal release rate by 150 minutes as shown in Tables 2 and 12. After gut decontamination, blood enemas did not alter basal ammonia production (Fig. 4).

Discussion

In order to study the mechanisms of increased ammonia production after upper gastrointestinal hemorrhage, many investigators have administered blood meals to dogs with chronic Eck-fistulas.[6,19,20] After gastric blood administration, a slow gradual rise in peripheral blood ammonia concentration usually occurred, suggesting that the colon was the source of the ammonia generated. However, the rate of portal ammonia generation was rarely quantitated and only peripheral blood ammonia concentrations were monitored. Moreover, relatively large volumes of blood (200–700 mL) were administered in many of the studies, which may have stimulated small bowel hyperperistalsis and delivered undigested blood to the colon. Such an experimental approach did not allow a distinction to be made between the ammonia produced in the upper and lower gastrointestinal tract.

In this study, we developed protocols that quantitated the rate of portal ammonia production in healthy, chronically catheterized animals. A small volume of

TABLE 10. *Effects of Gut Decontamination on Quantitative Stool Cultures (Mean ± SEM)*

	Colony Forming Units per Gram of Stool		
		Gut Decontamination	
Days of Antibiotic Therapy	Initial Cultures	5 Days	7 or 8 Days
Aerobic cultures (N = 6)	$1.24 \times 10^{10} \pm 6.95 \times 10^{9}$*	$3.36 \times 10^{8} \pm 1.73 \times 10^{8}$†	$2.85 \times 10^{8} \pm 1.69 \times 10^{6}$†
Anaerobic cultures (N = 6)	$4.21 \times 10^{10} \pm 9.89 \times 10^{9}$	$3.09 \times 10^{8} \pm 1.70 \times 10^{8}$‡	$2.38 \times 10^{8} \pm 1.56 \times 10^{8}$‡

* $p < 0.05$ when compared with control anaerobic colony counts by paired t-test.

† $p < 0.05$, ‡$p < 0.01$ when compared with control colony counts by Dunnett's test.

TABLE 11. *Average Values for Substrate Concentration, Blood Flow, and Gastrointestinal Exchange Measured in the Basal State After Gut Decontamination (Mean ± SEM)**

	Portal Concentration (μmol/L)	Arterial Concentration (μmol/L)	Portal–Arterial Difference (μmol/L)	Portal Blood Flow (mL/min/kg)	Gastrointestinal Exchange: Measured Flow (μmol/min/kg)	Gastrointestinal Exchange: Assumed Flow (μmol/min/kg)
Ammonia	306 ± 15‡ (12)	201 ± 15 (12)	104 ± 7†§ (12)	36 ± 5 (6)	4.18 ± 0.90 (6)	3.46 ± 0.49‡ (12)
Glutamine	709 ± 37 (12)	783 ± 43 (12)	−74 ± 14† (12)	36 ± 5 (6)	−2.14 ± 0.50 (6)	−2.05 ± 0.37 (12)
Glutamate	65 ± 3‡ (12)	58 ± 3‡ (12)	7 ± 1† (12)	36 ± 5 (6)	0.26 ± 0.03 (6)	0.21 ± 0.02 (12)

* Number of studies in parentheses.
† p < 0.01 when compared with 0.
(−) designates uptake, (+) designates release.
‡p < 0.05, §p < 0.001 by unpaired t-test when compared with basal values in animals not treated with antibiotics (Table 1).

blood was administered by meal and by enema (average volume approximately 120 mL), allowing us to differentiate between ammonia produced in the upper and lower gastrointestinal tract. The same quantity of ammonia was produced after blood was administered into the stomach or the colon, but the mechanisms involved appear different. For example, gastric administration resulted in a prompt peak (60 minutes) in intestinal ammonia production, whereas the time of peak production after blood enemas was severely delayed (150 minutes). This attenuated response after blood enemas was not due to the inability of bacteria to deaminate whole protein, for amino acid administration by enema produced similar rates of ammonia generation.

The small volume and caloric load contained in the blood meal was unlikely to alter the intestinal motility pattern of the small bowel.[21] The time of propagation of phase 3 of the migrating motor complex from the stomach to the terminal ileum in dogs ranges from 105 to 134 minutes,[22] a time too long to account for the rapid rise in ammonia production occurring after the blood meal if the ammonia were generated in the colon. The rise in portal concentration of ammonia after the blood meal mimicked absorption data of other markers of small bowel function, such as glucose or D-xylose.[23] Glutamine and glutamate absorption occurred at the same time ammonia production increased after blood meals. Because amino acids and peptides are almost exclusively absorbed in the upper jejunum by active transport processes,[24] this association also indicates that the small bowel was the source of the ammonia generated. The early rise in intestinal ammonia production appears to be due to the metabolism of ammoniagenic amino acids by enterocytes of the small intestine, a process that liberates ammonia.

The rise in portal and arterial glutamine concentrations after blood meals is consistent with the work of other investigators who have observed elevations in alpha-amino nitrogen and amino acids after a protein meal.[25,26] The diminished intestinal glutamine uptake observed after blood meals may be secondary to the inhibition of extraction of arterial glutamine by the bowel when glutamine and glutamate are present in the lumen.[9] The rise in portal glutamate concentration observed after blood meals was not observed in studies of amino acid metabolism after a horsemeat meal.[26] Our

TABLE 12. *Ammonia Concentrations, Blood Flow, and Gastrointestinal Ammonia Production After Blood Meals or Enemas After Gut Decontamination (Mean ± SEM)*

Time in Minutes	0	30	60	90	150	210
Blood meals (N = 6)						
Portal vein (μmol/L)	324 ± 12	456 ± 33*	484 ± 38†	499 ± 44†	490 ± 32†	419 ± 48
Arterial (μmol/L)	212 ± 16	235 ± 12	251 ± 11	248 ± 11	281 ± 13*	240 ± 29
PV-A (μmol/L)	109 ± 9	221 ± 35	232 ± 35*	249 ± 38*	213 ± 40	177 ± 31
Portal blood flow (N = 3) (mL/min/kg)	39 ± 10	46 ± 9	37 ± 1	42 ± 6	38 ± 5	36 ± 2
Ammonia production (μmol/min/kg)	3.91 ± 0.90	8.47 ± 2.07*	7.46 ± 0.99	8.44 ± 1.15*	7.11 ± 1.15	5.80 ± 1.12
Blood enemas (N = 6)						
Portal vein (μmol/L)	287 ± 26	330 ± 30	373 ± 32	330 ± 31	380 ± 31	306 ± 29
Arterial (μmol/L)	190 ± 25	97 ± 19	262 ± 12*	225 ± 6	252 ± 22	202 ± 21
PV-A (μmol/L)	100 ± 13	133 ± 18	133 ± 26	113 ± 18	115 ± 28	101 ± 21
Portal blood flow (N = 3) (mL/min/kg)	34 ± 3	30 ± 3	29 ± 4	35 ± 9	46 ± 19	43 ± 19
Ammonia production (μmol/min/kg)	3.02 ± 0.43	3.80 ± 0.50	3.63 ± 0.75	3.29 ± 0.56	3.90 ± 0.95	3.01 ± 0.9

* p < 0.05, ‡p < 0.01 when compared with T = 0 by Dunnett's test.

TABLE 13. *Portal, Arterial, PV-A Difference and Exchange of GLN and GLU After Blood Meals or Enemas After Gut Decontamination (Mean ± SEM)*

Time in Minutes	0	30	90	210
Blood meals (N = 6)				
Portal vein (μmol/L)				
GLN	686 ± 59	762 ± 68	713 ± 36	627 ± 44
GLU	63 ± 5	71 ± 8	79 ± 10	71 ± 10
Arterial (μmol/L)				
GLN	750 ± 72	807 ± 63	753 ± 41	692 ± 43
GLU	55 ± 5	58 ± 6	61 ± 8	57 ± 7
PV-A (μmol/L)				
GLN	−64 ± 18	−44 ± 19	−40 ± 19	−65 ± 27
GLU	7 ± 2	13 ± 3	17 ± 3	14 ± 4
Gastrointestinal exchange (μmol/min/kg)				
GLN	−1.44 ± 0.22	−1.58 ± 0.58	−1.61 ± 0.82	−2.12 ± 0.96
GLU	0.22 ± 0.04	0.46 ± 0.11	0.57 ± 0.73	0.53 ± 0.13
Blood enemas (N = 6)				
Portal vein (μmol/L)				
GLN	733 ± 47	710 ± 50	711 ± 56	701 ± 45
GLU	66 ± 3	67 ± 4	63 ± 5	66 ± 6
Arterial (μmol/L)				
GLN	816 ± 52	783 ± 48	766 ± 49*	701 ± 45*
GLU	61 ± 4	60 ± 4	57 ± 5	59 ± 5
PV-A (μmol/L)				
GLN	−83 ± 23	−73 ± 18	−55 ± 21	−62 ± 13
GLU	5 ± 1	7 ± 1	6 ± 1	7 ± 1
Gastrointestinal exchange (μmol/min/kg)				
GLN	−2.66 ± 0.64	−2.78 ± 0.49	−2.26 ± 0.52	−2.40 ± 0.54
GLU	0.20 ± 0.03	0.25 ± 0.04	0.22 ± 0.04	0.25 ± 0.06

* $p < 0.01$ when compared with T = 0 by Dunnett's test.

findings suggest that glutamate derived either from the blood meal or from the deamidation of glutamine is not entirely converted to other substances such as alanine because it is metabolized in the cells of the gastrointestinal tract of the small bowel.

Portal blood flow did not change after blood or amino acid meals, an observation consistent with previous reports that portal blood flow was unaltered after protein administration to awake dogs.[25] In contrast, portal blood flow increased after the instillation of protein hydrolysates into the duodenum of anesthetized dogs.[27] If such an increase in portal blood flow occurred in our studies but was undetected, the magnitude of this early rise in intestinal ammonia release after blood meals would be greater, not less, than the values reported.

After blood enemas, portal blood ammonia concentration gradually rose and peaked at 150 minutes. Although the total quantity of ammonia produced was generally comparable to that of the blood meal, the am-

TABLE 14. *Comparison of the Effects of Blood Meals or Enemas on Ammonia After Gut Decontamination (Mean ± SEM)*

Basal–Peak Responses	Meals	Enemas
Portal ammonia (μmol/L)	235 ± 36	108 ± 33*
Arterial ammonia (μmol/L)	94 ± 19	94 ± 21
PV-A difference (μmol/L)	202 ± 27	56 ± 23*
Gastrointestinal ammonia production (μmol/min/kg)	6.82 ± 0.59	2.02 ± 0.57†
Integrated area (μmol/kg)	652 ± 156	39 ± 94†

* $p < 0.01$, †$p < 0.001$ when responses to meals are compared with enemas by paired t-test.

Times of peak responses were not significantly different.

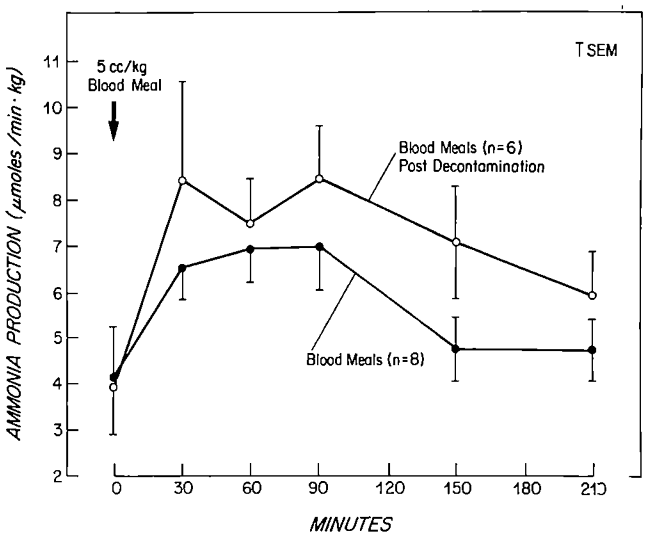

FIG. 3. Gastrointestinal ammonia production greatly increased in animals with and without gut decontamination after a blood meal.

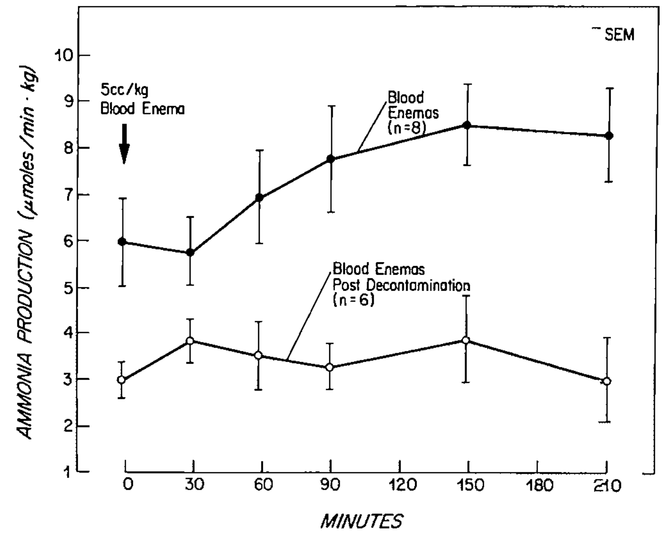

FIG. 4. The increase in ammonia production after blood enemas was greatly attenuated by intestinal decontamination.

monia production after blood enemas did not return to normal values by the end of the study. It is possible that additional measurements over several additional hours would have revealed persistent ammonia production for a longer period. Unlike the blood meals, there was no uptake of amino acids after the blood enemas. This is consistent with the proposed mechanism of intraluminal bacterial hydrolysis and slow diffusion of ammonia from the colon into the blood stream.

After 5–8 days of antibiotic administration, basal portal ammonia concentration, ammonia PV-A concentration difference, and basal ammonia production were all reduced, which are consistent with findings previously reported by others.[4] Antibiotic therapy abolished the gradual rise in ammonia production after blood enemas, which supports the concept that the delayed response in ammonia production after colonic blood administration is mediated by microbe enzymatic hydrolysis of the intraluminal nitrogen substrate found in the blood. However, antibiotic therapy did not attenuate the early rise in ammonia production after the blood meal, despite a greater than 93% reduction in the bowel microflora. Because of the relative paucity of bacteria in the upper gastrointestinal tract of mammals compared with the colon[28] and our failure to diminish the production from the upper gastrointestinal tract, it appears that micro-organisms play a relatively insignificant role in ammonia production by the small bowel. Gut decontamination decreased basal ammonia production of the intestinal tract in association with reducing the number of colonic bacteria. However, the small bowel ammonia production persisted after gastric blood administration, suggesting that nonmicrobial mechanisms are involved in this process.

An alternative hypothesis, however, has been advanced to explain the effect of intestinal antibiotics.[29] Van Leeuwen and associates have quantitated the rate of ammonia produced by isolated enterocytes and colocytes. Addition of lactulose or neomycin to these *in vitro* systems attenuated ammonia production. This response was observed in tissue harvested from either conventional or germ-free animals. The authors conclude that these substances reduce ammonia production by interfering with intracellular glutamine metabolism. Although our *in vivo* studies were not designed to parallel these *in vitro* experiments, we cannot exclude this hypothesis as a possible explanation for the attenuation of ammonia production in the decontaminated animals after blood enemas. However, since ammonia production from the upper gastrointestinal tract was unaffected by antibiotic administration, this direct effect on enterocyte metabolism did not occur in our animals. It should be noted that lactulose was not given as part of our decontamination regimen.

Gut decontamination had no effect on basal intestinal exchange of glutamine and glutamate. Although glutamine concentrations were not altered, both arterial and portal glutamate concentrations were diminished. The hepatic synthesis of glutamate depends on the availability of its precursors ammonia and alpha-ketoglutarate. The diminished glutamate levels may reflect the decrease in the gastrointestinal ammonia production.[30] After the administration of the blood meal to decontaminated animals, the absorption of glutamine and glutamate was attenuated. The effect may be related to the administration of antibiotics by the enteral route. It has been reported that neomycin decreases the concentrations of selected enzymes within the enterocyte.[29] Neomycin administration is also associated with a reversible malabsorption syndrome, which may explain the failure of glutamine and glutamate to rise after the blood meal.[31] Although the specific role of these antibiotics in decreasing the portal concentrations of glutamine after a blood meal is not known, the early rise in intestinal ammonia production in decontaminated animals after a blood meal suggests that glutamine is absorbed and utilized by the enterocyte to generate ammonia. Further studies are needed to define the interaction among intraluminal antibiotics, enterocyte metabolism, and intestinal ammonia production.

It is believed that hyperammonemia plays some role in the cause of hepatic encephalopathy, although the exact relationship between elevated ammonia concentration in arterial blood and central nervous system dysfunction remains unknown. However, administration of agents that reduce the microbial flora or alter intraluminal ammonia production is common clinical practice. Although this treatment may be effective therapy for the ammonia produced by the colon, it has little impact on ammonia produced by the small intestine. Therapy that specifically decreases small bowel ammonia production is necessary if hyperammonia after upper gastrointestinal hemorrhage is to be controlled.

In summary, intestinal ammonia production increases within the first 60 minutes after a blood meal. This response was mimicked by the gastric administration of ammoniagenic amino acids. The increased ammonia production after blood meals was associated with amino acid absorption, which indicates the small intestine was participating in this response. In contrast, blood administered by enema resulted in a gradual rise in ammonia production. This response was not due to a lack of predigestion of protein precursors that are presented to the colon from the upper gastrointestinal tract, for amino acid enemas elicited responses similar to blood instillation. Gut decontamination reduced basal ammonia production and ablated the rise in ammonia production after colonic blood administration. Gut decontamination had no effect on ammonia production after a blood meal.

The increased ammonia production after upper gastrointestinal hemorrhage results from the generation of ammonia by both the small intestine and colon. The enterocytes of the small bowel absorb and metabolize ammoniagenic amino acids derived from blood proteins and produce ammonia. Bacteria of the colon hydrolyze the blood reaching the distal bowel and liberate ammonia. Although gut decontamination may reduce ammonia production by the colon, it is not specific therapy directed toward enterocyte amino acid metabolism and therefore does not alter the ammonia produced by the small intestine.

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Studies on the Possible Role of Thyroid Hormone in Altered Muscle Protein Turnover During Sepsis

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Five days after thyroidectomy (Tx) or sham-Tx in young male Sprague-Dawley rats, sepsis was induced by cecal ligation and puncture (CLP). Control animals underwent laparotomy and manipulation of the cecum without ligation or puncture. Sixteen hours after CLP or laparotomy, protein synthesis and degradation were measured in incubated extensor digitorum longus (EDL) and soleus (SOL) muscles by determining rate of ^{14}C-phenylalanine incorporation into protein and tyrosine release into incubation medium, respectively. Triiodothyronine (T_3) was measured in serum and muscle tissue. Protein synthesis was reduced by 39% and 22% in EDL and SOL, respectively, 16 hours after CLP in sham-Tx rats. The response to sepsis of protein synthesis was abolished in Tx rats. Protein breakdown was increased by 113% and 68% in EDL and SOL, respectively, 16 hours after CLP in sham-Tx animals. The increase in muscle proteolysis during sepsis was blunted in hypothyroid animals and was 42% and 49% in EDL and SOL, respectively. T_3 in serum was reduced by sepsis, both in Tx and sham-Tx rats. T_3 in muscle, however, was maintained or increased during sepsis. Abolished or blunted response of muscle protein turnover after CLP in hypothyroid animals may reflect a role of thyroid hormones in altered muscle protein metabolism during sepsis. Reduced serum levels of T_3, but maintained or increased muscle concentrations of the hormone, suggests that increased T_3 uptake by muscle may be one mechanism of low T_3 syndrome in sepsis, further supporting the concept of a role for thyroid hormone in metabolic alterations in muscle during sepsis.

ACCELERATED BREAKDOWN and inhibited synthesis of skeletal muscle protein have been reported both in hyperthyroidism[1-4] and sepsis.[5-8] This may seem paradoxical, since circulating levels of thyroid hormones are reduced in critically ill and septic patients,[9,10] and may indicate that thyroid hormones are not involved in the pathogenesis of altered muscle protein turnover in sepsis. Recent studies, however, suggested that one mechanism of low serum concentrations of thyroid hormones in sepsis may be enhanced tissue uptake.[11,12] Thus, total cellular and hepatic uptake of thyroxine (T_4) was increased in septic monkeys,[11] and concentration of triiodothyronine (T_3) was maintained or increased in kidney and liver tissue during endotoxemia in rats, despite decreased circulating T_3 levels.[12]

T_3 concentrations in muscle tissue during sepsis have not been reported, and it is not known if thyroid hormone plays a role in altered muscle protein metabolism in this condition. The purpose of this investigation was to study muscle T_3 levels during sepsis and to measure protein turnover rates in incubated skeletal muscles from septic euthyroid and hypothyroid rats. Preliminary results of this study were presented previously.[13]

Materials and Methods

Thyroidectomy (Tx) or sham thyroidectomy (sham-Tx) was performed in young, male Sprague-Dawley rats, weighing 45–50 g (Zivic-Miller, Allison Park, PA). To compensate for possible damage to the parathyroid glands during Tx, rats received drinking water supplemented with 1% calcium lactate after Tx. Small animals were used because they have thin extensor digitorum longus (EDL) and soleus (SOL) muscles, enabling measurement of protein turnover in incubated muscles.[14]

One group of rats was killed 5 days after Tx or sham-Tx for determination of T_3 and calcium levels in serum. In other rats, sepsis was induced between 5:00 P.M. and 6:00 P.M. on the 5th day after Tx or sham-Tx, and 16 hours later, T_3 in muscle and serum and protein turnover rates in incubated EDL and SOL muscles were

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measured. Only T_3 was determined because this is biologically the most active form of thyroid hormones.

Sepsis was induced by cecal ligation and puncture (CLP) as described previously.[15] Under light ether anesthesia, laparotomy was performed and the cecum was ligated and punctured twice with an 18-gauge needle. Nonseptic control rats had sham operation, in which a laparotomy was performed and the cecum was manipulated but not ligated or punctured. All rats received saline (5 mL/100 g) subcutaneously on the back for resuscitation and were fasted with free access to water after the operative procedures. After 16 hours, four groups of rats were studied, *i.e.*, sham-Tx controls, sham-Tx CLP, Tx controls, and Tx CLP. All animals, from which muscles were harvested, weighed 70 g or less.[14]

Measurement of Protein Synthesis and Degradation in Incubated Skeletal Muscles

Under light ether anesthesia, EDL and SOL muscles were dissected with intact tendons, weighed, and preincubated for 30 minutes in 3 mL of a medium consisting of Krebs-Henseleit bicarbonate buffer (pH 7.4) with glucose (10 mM). The medium was saturated with O_2:CO_2 (95:5) and incubation was performed in a shaking water bath at 37 C. After preincubation the muscles were gently blotted and transferred to fresh medium. For the study of protein synthesis, the medium was supplemented with [^{14}C]-phenylalanine (0.5 mM; 0.05 uCi/mL) and the amount of amino acid incorporated into protein during incubation for 2 hours (μmol Phe × gww^{-1} × $2h^{-1}$) was determined as described in detail elsewhere.[8] For the study of protein degradation, the medium was supplemented with cycloheximide (0.5 mM) to prevent reincorporation of amino acids, and protein degradation rate was estimated from amount of tyrosine released into the incubation medium during 2 hours (μmol Tyr × gww^{-1} × $2h^{-1}$). Tyrosine was determined according to Waalkes and Udenfriend.[16] This method for measurement of protein degradation rate was described previously.[17–19] Since tyrosine is not synthesized or metabolized by skeletal muscle, and tissue concentration of free tyrosine remained constant during incubation, both in normal and septic muscles,[7] it is possible to estimate protein degradation rate by measuring release of tyrosine into the incubation medium.

Determination of Serum and Muscle T_3 Levels

Under light ether anesthesia, blood was drawn by heart puncture and one SOL muscle was dissected as described above. The muscle was immediately frozen on dry ice, weighed (muscle weights varied between 25 and 30 mg) and homogenized in 0.15 mL of saline with 10^{-3} mM propylthiouracil (Sigma, St. Louis, MO) at 0–4 C in a micro-homogenizer (Kontes Glassware, Vineland, NJ). A small amount of ^{125}I-T_3 was added to the homogenate for determination of recovery. Ethanol (0.3 mL of 96% ethanol) was added to the homogenate and thoroughly mixed on a Vortex Mixer (American Scientific Products, McGaw Park, IL) for 1 minute. After centrifugation (1500 g for 20 minutes) the extraction of the pellet with ethanol was repeated twice. The supernatants were then pooled and recentrifuged at 1500 g for 20 minutes. An aliquot of the ethanol extract was dried under a stream of nitrogen. The residue was dissolved in 50 μL of T_3 free serum and counted to determine recovery, which was 91 ± 2% (N = 44).

TABLE 1. *T_3 and Calcium Concentrations in Serum 5 Days after Tx or Sham-Tx in Rats*

	Sham-Tx (N = 6)	Tx (N = 6)
T_3 (ng/dL)	118 ± 7.9	46 ± 2.7*
Calcium (mg/dL)	10.2 ± 0.22	8.1 ± 0.17*

* $p < 0.01$ *vs.* sham-Tx (Wilcoxon rank sum test).

For determination of T_3 in blood serum and muscle extract, a radioimmunoassay was used (Diagnostic Products Corporation, Los Angeles, CA). To maximize sensitivity of the assay, the following modified protocol was established: 50 μL of T_3 standard, serum sample, or muscle extract was incubated with 50 μL of ^{125}I-T_3 and 50 μL of T_3 antiserum (diluted twice with water) at 4 C for 16–18 hours, followed by addition of 500 μL of goat antirabbit IgG, centrifugation, and counting of the precipitate. The minimum detection limit of the assay was 2.5 pg per tube with an interassay coefficient of variation less than 6.3%.

Statistics

Results are presented as mean ± SEM. Unless stated otherwise, significant differences between group means were determined by analysis of variance (ANOVA) followed by Duncan's multiple range test. A p value less than 0.05 was considered significant.

Results

Serum T_3 5 days after sham-Tx was 118 ± 7.9 ng/dL, which is in line with previous studies in young Sprague-Dawley rats,[20] but higher than reported in bigger rats.[12] Five days after Tx, T_3 in serum was reduced to about one third of control value (Table 1). Despite the fact that thyroidectomized animals received drinking water supplemented with calcium lactate, serum calcium was reduced 5 days after Tx (Table 1).

The survival rate was approximately 20% 16 hours after CLP with no significant difference between Tx and

TABLE 2. *Body Temperature (C) 16 Hours after Sham-laparotomy (Control) or CLP in Euthyroid (Sham-Tx) and Hypothyroid (Tx) Rats**

	Control	CLP
Sham-Tx	37.8 ± 0.15 (8)	37.0 ± 0.51 (8)
Tx	36.9 ± 0.29 (8)	35.0 ± 0.49† (13)

* Numbers in parentheses indicate number of rats.
† $p < 0.05$ *vs.* all other groups (ANOVA).

sham-Tx rats. There was no mortality rate among control (sham-CLP) rats. All surviving septic rats showed clinical signs of illness in the form of diarrhea, piloerection, and exudate around the eyes, with no apparent differences between euthyroid and hypothyroid rats.

Body temperature was somewhat lower in septic, euthyroid rats than in nonseptic euthyroid rats (Table 2), although the difference was not statistically significant. Similar results were reported in recent studies from this laboratory,[7,8] and probably reflect the small-sized rats used in this study. Regulation of body temperature is different in small rodents than in bigger animals due to the relatively high surface area to volume ratio,[21] which probably explains why sepsis was not associated with hyperthermia in this study. As expected, body temperature was lower in hypothyroid than in euthyroid rats, and temperature was further decreased in hypothyroid, septic rats (Table 2).

Serum T_3 was significantly reduced 16 hours after CLP in sham-Tx rats (Fig. 1), confirming previous results of a low T_3 syndrome after injury and sepsis.[9,10,12] Also, in hypothyroid rats (Tx), serum T_3 was significantly decreased during sepsis (Fig. 1).

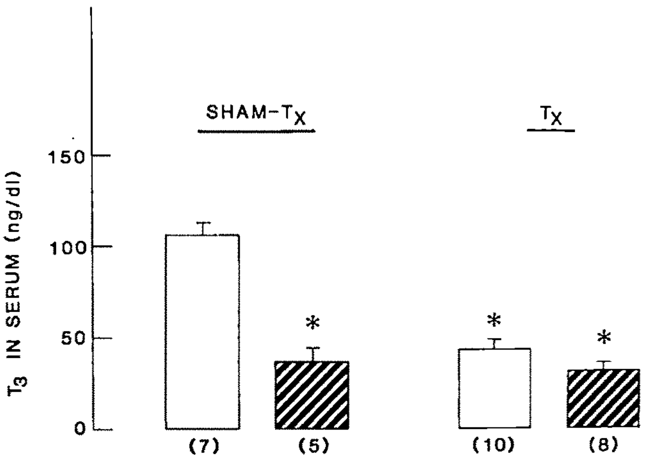

FIG. 1. Serum T_3 in sham-Tx and Tx rats 16 hours after sham-CLP (open bars) or CLP (hatched bars). Numbers in parentheses indicate number of rats. * $p < 0.05$ *versus* sham-Tx, nonseptic group. The difference between nonseptic and septic groups in Tx rats was also statistically significant ($p < 0.05$ by ANOVA).

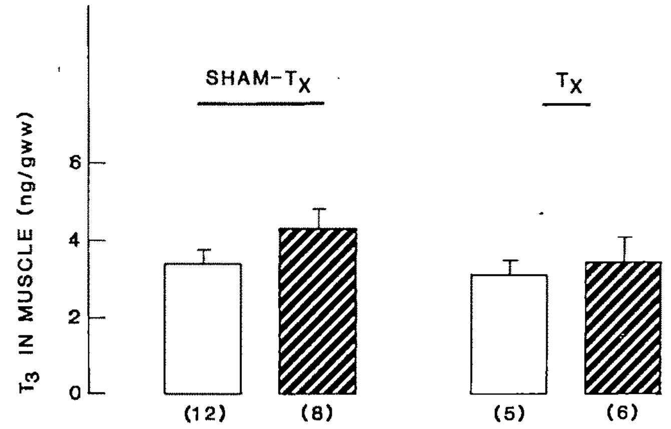

FIG. 2. Concentration of T_3 in SOL muscles from sham-Tx and Tx rats 16 hours after sham-CLP (open bars) or CLP (hatched bars). Numbers in parentheses indicate number of rats.

T_3 in SOL muscle from euthyroid (sham-Tx) control rats was 3.42 ± 0.22 ng/g tissue, which is in agreement with T_3 concentrations in red muscle, reported previously.[22] The mean value of muscle T_3 was 25% higher in septic, euthyroid rats than in nonseptic, euthyroid rats (Fig. 2). This difference, however, was not statistically significant by ANOVA. The range of T_3 concentrations in septic muscles was 2.67–6.06 ng/g and in nonseptic muscles was 2.38–4.71 ng/g. Muscle T_3 in hypothyroid control and septic rats was similar to the hormone concentration in muscle from euthyroid, nonseptic rats (Fig. 2).

Protein synthesis rate in incubated EDL and SOL muscles was reduced by 39% and 22%, respectively, 16 hours after CLP in euthyroid rats (Table 3). In previous studies, both increased[23,24] and reduced[6] synthetic rates were reported in sepsis. In a recent communication from this laboratory, protein synthesis in incubated rat EDL muscles was unchanged, whereas synthetic rate in SOL muscles was reduced 8 hours and 16 hours after CLP, although not significantly.[8] Thus, the effect of sepsis on muscle protein synthesis is not as consistent as the stimulating effect on protein breakdown. In nonseptic, hypothyroid rats, protein synthesis rate was reduced in EDL but was not altered in SOL (Table 3). In contrast to euthyroid rats, no significant reduction of protein synthesis occurred in EDL or SOL during sepsis in Tx rats (Table 3).

Protein breakdown rate in incubated EDL and SOL muscles was increased by 113% and 68%, respectively, 16 hours after CLP in euthyroid rats (Table 4), similar to previous reports from this laboratory.[7,8] Protein breakdown rates in EDL and SOL muscles in nonseptic, hypothyroid rats were similar to control values in sham-Tx rats. In other studies, reduced protein degradation was observed in animals in which Tx resulted in nonmea-

TABLE 3. *Protein Synthesis Rates (μmol Tyr × gww^{-1} × $2h^{-1}$) in Incubated EDL and SOL Muscles*

	Sham-Tx		Tx	
	Control (8)	CLP (8)	Control (4)	CLP (8)
EDL	0.094 ± 0.006	0.057 ± 0.002* (−39%)	0.068 ± 0.009†	0.064 ± 0.004
SOL	0.142 ± 0.011	0.111 ± 0.007* (−22%)	0.148 ± 0.014	0.128 ± 0.004

* $p < 0.05$ *vs.* control; †$p < 0.05$ *vs.* control in sham-Tx group.

surable serum T_3 levels.[25] The increase in muscle proteolysis during sepsis was blunted in the hypothyroid rats compared with the increase seen in euthyroid rats, and was 42% and 49% in EDL and SOL, respectively (Table 4). The difference in proteolytic rates between septic hypothyroid and septic euthyroid rats was statistically significant.

Discussion

This study demonstrated that the sepsis-induced inhibition of muscle protein synthesis and increase in muscle protein breakdown were abolished or blunted in hypothyroid rats. The results may be consistent with the hypothesis that thyroid hormones play a role in altered muscle protein metabolism during sepsis, although other interpretations must be considered as well. The data also showed that changes in serum T_3 levels did not reflect alterations in muscle concentrations of the hormone, since T_3 in muscle was unchanged or increased after Tx and during sepsis, despite reduced serum levels.

In a previous study, serum T_4 was reduced to 13% of control values 3 days after thyroidectomy in rats.[26] Since disappearance time from serum of T_3 is shorter than that of T_4,[27] our results of serum T_3 levels 5 days after Tx, *i.e.*, approximately one third of control values, suggest that the thyroid gland was not completely removed in our rats. This probably reflected technical difficulties due to the small size of the animals, further supported by the damage to the parathyroid glands, as indicated by reduced serum calcium levels.

Survival rates were not significantly different in septic euthyroid and hypothyroid rats in this study. In a previous report, the survival rate after CLP in rats was reduced from 65% to 30% in hypothyroid rats.[26] Comparison of these results is difficult, however, because in that study bigger rats were used and sepsis was induced 2 weeks after Tx, at which time serum levels of thyroid hormones were too low to be measurable.[26]

Different mechanisms of reduced circulating levels of thyroid hormones after injury and sepsis were suggested previously, *e.g.*, reduced thyroid function,[27,28] defective binding of the hormones to carrier proteins,[29] and an impaired 5′-deiodination of T_4 to T_3.[30] Accelerated peripheral disposal of thyroid hormones was demonstrated during bacterial infections and fever,[31] possibly reflecting increased deiodination of the hormones by phagocytic cells[32] or increased uptake in different tissues.[11,12] The increased T_3 concentrations in septic muscle in the current study, although not statistically significant, may reflect enhanced uptake of the hormone in skeletal muscle during sepsis. Evidence of specific and concentrative transport systems for intracellular uptake of T_3 in different tissues was presented recently.[33]

Another mechanism for maintaining or elevating muscle T_3 levels in sepsis might be an increased conversion of T_4 to T_3. Results demonstrating that T_4 to T_3 conversion occurs in skeletal muscle were reported previously.[34] The same study, however, showed that the amount of T_3 taken up by muscle during a 2-hour period was approximately 200 times greater than the amount converted from T_4 during the same period. Thus, alterations in cellular uptake are probably more important than changes in T_4 to T_3 conversion for the regulation of muscle T_3 levels. Based on the T_3 concen-

TABLE 4. *Protein Degradation Rates (μmol Tyr × gww^{-1} × $2h^{-1}$) in Incubated EDL and SOL Muscles*

	Sham-Tx		Tx	
	Control (8)	CLP (8)	Control (8)	CLP (13)
EDL	0.290 ± 0.016	0.618 ± 0.049* (+113%)	0.294 ± 0.022	0.417 ± 0.024*† (+42%)
SOL	0.377 ± 0.021	0.633 ± 0.028* (+68%)	0.278 ± 0.013	0.413 ± 0.035*† (+49%)

* $p < 0.05$ *vs.* control; †$p < 0.05$ *vs.* CLP in sham-Tx group.

trations in serum and muscle found in this study, the calculated amount of T_3 in the total muscle pool was 20–30 times greater than total serum T_3, suggesting that even a small alteration in muscle T_3 uptake could greatly influence serum levels.

The current observation that muscle concentration of T_3 was maintained 5 days after thyroidectomy is in agreement with a recent report by Obregon et al.[35] In that study thyroid hormones were clearly detectable in different tissues, including muscle, up to 4 months after thyroidectomy in rats. Thus, not only does muscle contain a much larger pool of thyroid hormones, but the disappearance rate of the hormones is also substantially lower in muscle than in serum. This further suggests that consideration of tissue levels, in addition to serum concentrations, is important when the metabolic effects of thyroid hormones are studied.

Possible mediator(s) and mechanism(s) of accelerated muscle protein breakdown in sepsis have been extensively studied in recent years. Reports by Clowes et al. suggested that a circulating peptide called proteolysis-inducing factor (PIF), which is probably a split product of interleukin-1 (IL-1), is the mediator of enhanced muscle proteolysis after injury and sepsis.[5,36,37] Studies by Watters et al., however, did not confirm a role of IL-1 or PIF for accelerated muscle protein breakdown,[38] but suggested that the combined effect of the catabolic hormones cortisol, glucagon, and epinephrine may be responsible for metabolic alterations in trauma and sepsis.[39] It is possible that different types of stimuli are required for the full manifestation of host responses to severe injury and infection.[40]

The result in this study of blunted increase in muscle protein breakdown in hypothyroid rats may be interpreted as indicating that thyroid hormones play a role in sepsis-induced muscle proteolysis. The fact that protein breakdown was increased to some extent in septic, hypothyroid rats, in which muscle T_3 was not elevated, suggests, however, that thyroid hormones are not a major mediator of protein breakdown in sepsis. It is possible that the results reflected an interaction between thyroid hormones and other metabolic mediators, such as catecholamines.[41,42]

The mechanism of reduced protein synthesis in sepsis has not been extensively studied, probably reflecting that the response of protein synthesis is not consistent, and that the major effect of sepsis on muscle is a dramatic acceleration of protein breakdown. Also, in the hyperthyroid state, the major event in skeletal muscle was an acceleration of proteolysis, whereas protein synthesis was unchanged,[2,3] increased,[43] or reduced.[4]

The inability of the hypothyroid rats to respond normally to sepsis in the current study is in agreement with a recent report by Moley et al.[26] In that study, total body oxygen consumption was increased by 13% during early sepsis in normal rats, but was depressed by 20% in septic, hypothyroid rats. Liver blood flow, which increased after induction of sepsis in euthyroid rats, was unchanged in hypothyroid rats. Hepatic mitochondrial respiratory control ratio was also affected by the hypothyroid state.[26] Thus, thyroid hormones may be of importance for various metabolic responses to sepsis. Since serum concentrations of thyroid hormones are reduced both in sepsis and after Tx, but the metabolic changes are opposite, the interaction between thyroid hormone and sepsis may be best explained by tissue levels of the hormone.

Although the current results suggest a role of thyroid hormone in accelerated muscle proteolysis during sepsis, other interpretations of the results may also be considered. Increased protein breakdown after the addition of calcium *in vitro* to incubated rat skeletal muscles was reported previously.[44] Hence, it could be argued that the reduced protein degradation in septic, hypothyroid rats reflected reduced serum calcium levels. A recent study demonstrated, however, that the effect of calcium on muscle protein breakdown is mainly an *in vitro* phenomenon, and muscle protein degradation rates were similar in patients with different serum calcium levels.[45]

In addition to lower serum concentration of T_3 and calcium, body temperature was reduced in thyroidectomized rats. In a recent study, protein degradation in incubated rat skeletal muscles was decreased when the temperature of the incubation medium was reduced.[46] It is not likely, however, that the blunted increase in muscle proteolysis in the hypothyroid rats was due to reduced body temperature, since in recent studies we found that protein breakdown was greatly increased in septic rats, despite hypothermia.[7,8] Similarly, results were reported suggesting that the hypermetabolic response to sepsis was independent of changes in body temperature.[47]

Tx is known to reduce the amount of growth hormone in the pituitary and serum of rats.[48] Protein turnover in skeletal muscle is influenced by growth hormone.[49] However, since serum concentration of growth hormone remained within control range for at least 7 days after Tx,[48] it is not likely that results in the current study were caused by altered growth hormone levels.

Decreased blood volume and cardiac output was reported in hypothyroidism.[50] Thus, despite that all animals were volume resuscitated after induction of sepsis, it is possible that inability to develop a hyperdynamic phase during sepsis might be a reason for the blunted metabolic response in hypothyroid rats.

In conclusion, the current study suggests that thyroid hormones play a role in altered muscle protein turnover during sepsis. Further experiments are required, however, to rule out the possibility that the results reflected other effects of Tx than reduced T_3 levels. In future studies, the interaction between T_3 and other possible mediators of protein breakdown in sepsis, such as IL-1 and the catabolic hormones, would be of interest to elucidate.

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When
B fragilis
is the
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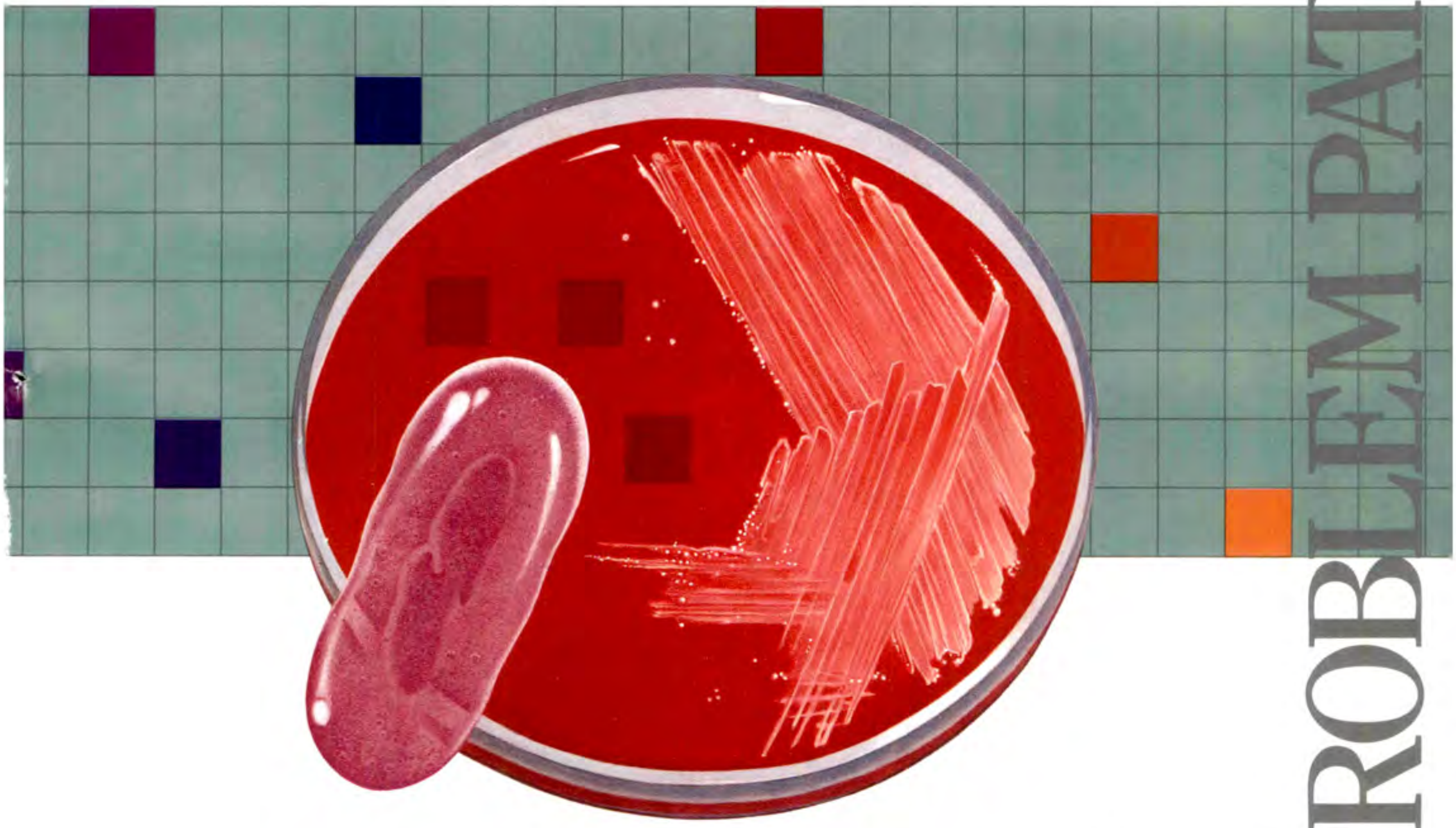

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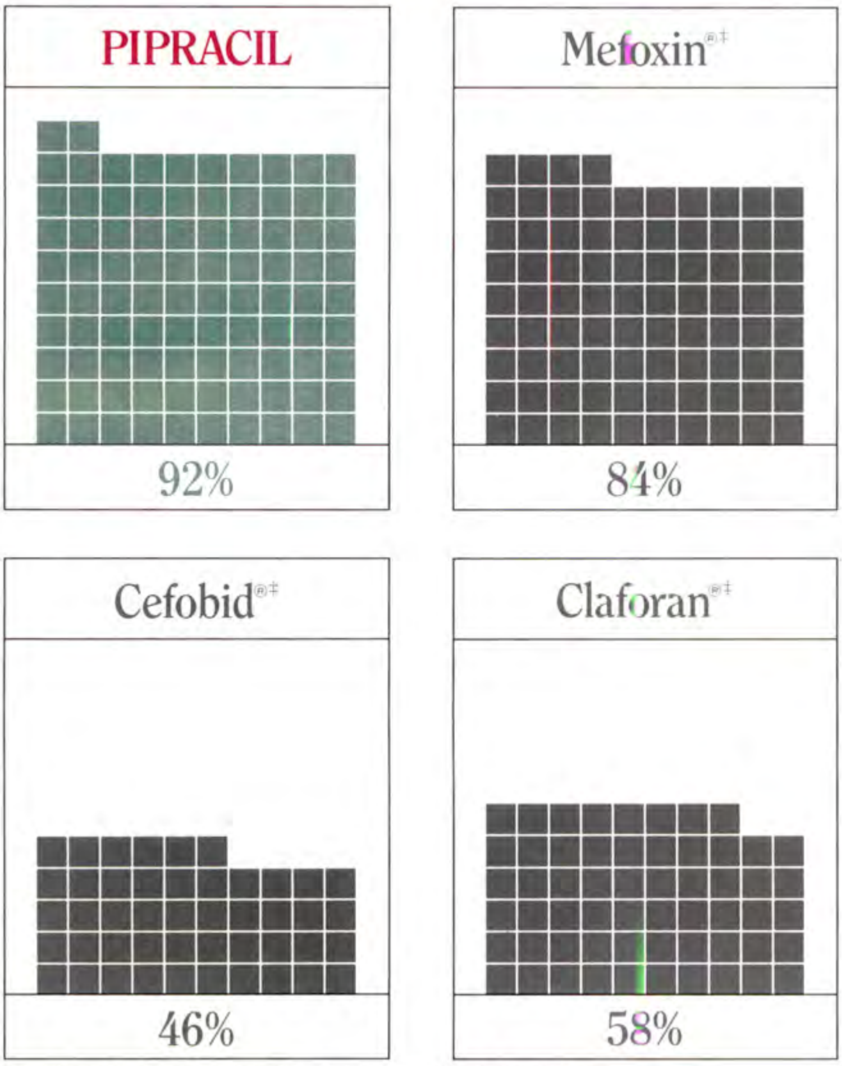

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*Although a useful guide, *in vitro* activity does not necessarily correlate with clinical response.

†1981, 1982, 1983.

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INDICATIONS AND USAGE: Therapeutic. PIPRACIL is indicated for the treatment of the following serious infections caused by susceptible strains of the designated organisms: Intra-abdominal, urinary tract, gynecologic, lower respiratory tract, skin and skin structure, bone and joint, gonococcal infections, and septicemia.

Prophylaxis. PIPRACIL is also indicated for prophylactic use in surgery including intra-abdominal (gastrointestinal and biliary) procedures, vaginal hysterectomy, and cesarean section.

CONTRAINDICATIONS: A history of allergic reactions to any of the penicillins and/or cephalosporins.

WARNINGS: Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients receiving therapy with penicillins. These reactions are more apt to occur in persons with a history of sensitivity to multiple allergens.

There have been reports of patients with a history of penicillin hypersensitivity who have experienced severe hypersensitivity reactions when treated with a cephalosporin. Before initiating therapy with PIPRACIL® sterile piperacillin sodium, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, and other allergens. If an allergic reaction occurs during therapy with PIPRACIL, the antibiotic should be discontinued. The usual agents (antihistamines, pressor amines, and corticosteroids) should be readily available. SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN AND INTRAVENOUS CORTICOSTEROIDS AND AIRWAY MANAGEMENT INCLUDING INTUBATION SHOULD ALSO BE ADMINISTERED AS NECESSARY.

PRECAUTIONS: General. While PIPRACIL possesses the characteristic low toxicity of the penicillin group of antibiotics, periodic assessment of organ system functions including renal, hepatic, and hematopoietic during prolonged therapy is advisable. Bleeding manifestations have occurred in some patients receiving β-lactam antibiotics including piperacillin. These reactions have sometimes been associated with abnormalities of coagulation tests such as clotting time, platelet aggregation, and prothrombin time and are more likely to occur in patients with renal failure. If bleeding manifestations occur, the antibiotic should be discontinued and appropriate therapy instituted.

The possibility of the emergence of resistant organisms which might cause superinfections should be kept in mind, particularly during prolonged treatment. If this occurs, appropriate measures should be taken.

As with other penicillins, patients may experience neuromuscular excitability or convulsions if higher than recommended doses are given intravenously.

PIPRACIL is a monosodium compound containing 1.85 milliequivalents of Na^+ per gram. This should be considered when treating patients requiring restricted salt intake. Periodic electrolyte determinations should be made in patients with low potassium reserves, and the possibility of hypokalemia should be kept in mind with patients who have potentially low potassium reserves and who are receiving cytotoxic therapy or diuretics.

Antimicrobials used in high doses for short periods to treat gonorrhea may mask or delay the symptoms of incubating syphilis. Therefore, prior to treatment, patients with gonorrhea should also be evaluated for syphilis. Specimens for darkfield examination should be obtained from patients with any suspected primary lesion and serologic tests should be performed. In all cases where concomitant syphilis is suspected, monthly serological tests should be made for a minimum of four months.

As with other semisynthetic penicillins, PIPRACIL therapy has been associated with an increased incidence of fever and rash in cystic fibrosis patients.

Drug Interactions. The mixing of PIPRACIL with an aminoglycoside *in vitro* can result in substantial inactivation of the aminoglycosides.

Pregnancy—Pregnancy Category B. Although reproduction studies in mice and rats performed at doses up to four times the human dose have shown no evidence of impaired fertility or harm to the fetus, safety of PIPRACIL use in pregnant women has not been determined by adequate and well-controlled studies. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. It has been found to cross the placenta in rats.

Nursing Mothers. Caution should be exercised when PIPRACIL is administered to nursing mothers. It is excreted in low concentrations in milk.

Pediatric Use. Dosages for children under the age of 12 have not been established. The safety of PIPRACIL in neonates is not known. In dog neonates dilated renal tubules and peritubular hyalinization occurred following administration of PIPRACIL.

ADVERSE EFFECTS: PIPRACIL is generally well tolerated. The most common adverse reactions have been local in nature, following intravenous or intramuscular injection. The following adverse reactions may occur:

Local Reactions. Thrombophlebitis (4%), pain, erythema, and/or induration at the injection site (2%) and, less frequently, ecchymosis, deep vein thrombosis, hematomas.

Gastrointestinal. Diarrhea and loose stools (2%); less frequently, vomiting, nausea, increases in liver enzymes (LDH, SGOT, SGPT), hyperbilirubinemia, cholestatic hepatitis, bloody diarrhea, and, rarely, pseudomembranous colitis.

Hypersensitivity Reactions. Anaphylactoid Reactions (see WARNINGS). Rash (1%); less frequently, pruritus, vesicular eruptions, positive Coombs tests.

Renal. Elevations of creatinine or BUN and, rarely, interstitial nephritis.

Central Nervous System. Headache, dizziness, fatigue.

Hemic and Lymphatic. Reversible leukopenia, neutropenia, thrombocytopenia, and/or eosinophilia have been reported. As with other β-lactam antibiotics, reversible leukopenia (neutropenia) is more apt to occur in patients receiving prolonged therapy at high dosages or in association with drugs known to cause this reaction.

Serum Electrolytes. Individuals with liver disease, or individuals receiving cytotoxic therapy or diuretics, were reported rarely to demonstrate a decrease in serum potassium concentrations with high doses of piperacillin.

Skeletal. Rarely, prolonged muscle relaxation.

Other. Superinfection, including candidiasis. Hemorrhagic manifestations.

Rev. 5/86

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Lymphocyte Participation in Wound Healing

Morphologic Assessment Using Monoclonal Antibodies

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To investigate lymphocyte participation in wound healing, the migration of T lymphocyte subsets into healing wounds and subcutaneously implanted polyvinyl alcohol sponges was studied. Frozen sections of 5-, 7-, and 10-day-old incisional wounds and sponges from Lewis rats were stained with mouse anti-rat monoclonal antibodies. Cellular staining to OX1 (all leucocyte), W3/25 (helper/effector T lymphocytes), and OX8 (suppressor/cytotoxic T lymphocytes) was quantitated in two arbitrarily defined areas based on maximal cellular infiltration: (1) the superficial wound, down to and including the papillary dermis, and (2) the deep wound, the reticular dermis. Five-day wounds were significantly more cellular than 10-day wounds in the deep portion ($p < 0.05$) and somewhat more cellular in the superficial section ($p < 0.10$). Approximately 2:1 W3/25 to OX8 ratios were noted for wound strips on all days. At 5 and 10 days there are twice as many W3/25 and OX8 labeled cells in the deep wound as in the superficial portion. At 7 days there is a peak in surface W3/25 and OX8 lymphocytes, whereas the deep population remains constant. Seven- and 10-day sponge granulomas demonstrate ratios similar to the wound strips (5-day sponge lymphocytic infiltration was insufficient to count). The data demonstrate that lymphocyte subpopulation participation in wound healing is a dynamic and distinctive process.

THE NORMAL HEALING OF WOUNDS involves a cascade of cellular events. Although lymphocytes predictably migrate into wounds,[1] their role in the healing process is poorly defined. Antigen-stimulated lymphocytes produce lymphokines, which have been shown to influence *in vitro* fibroblast replication and collagenous protein synthesis.[2,3] Evidence also exists that alterations in host immune response can alter the course of fibroplasia after wounding.[4,5] However, direct *in vivo* proof of lymphocyte participation in wound healing is lacking.[6]

The purpose of this experiment was to elucidate the role of lymphocytes in wound healing by characterizing morphologically the T lymphocyte subpopulations that migrate into wounds at various stages of healing. The aims of this study were: (1) to determine the ratio of T helper/effector:T suppressor/cytotoxic lymphocytes present in wounds, and (2) to study the dynamics of T lymphocyte subsets during wound healing. This was accomplished by using specific monoclonal antibodies to examine T lymphocyte subsets in a rat wound healing model.

Materials and Methods

Male Lewis rats (Harlan Sprague-Dawley, Walkersville, MD), weighing 250–300 g were individually housed at constant temperature (25 ± 1 C) and humidity (40–50%). All rats were fed a complete laboratory chow, Teklad 4% Mouse-Rat Diet (Teklad Test Diets, Madison, WI) and tap water *ad libitum*. The rats were allowed at least 1 week of acclimatization to our laboratory conditions before being used in the experiments.

Under pentobarbital anesthesia (4 mg/kg body weight i.p.) the backs of the rats were shaved and then scrubbed with povidone iodine solution. Using clean conditions, 7-cm dorsal midline wounds were made sharply down to the level of the fascia. At the upper poles of the wound, two sterile, moistened polyvinyl alcohol sponges were placed into subcutaneous pockets. The wounds were then closed with seven interrupted 4-0 stainless steel sutures.

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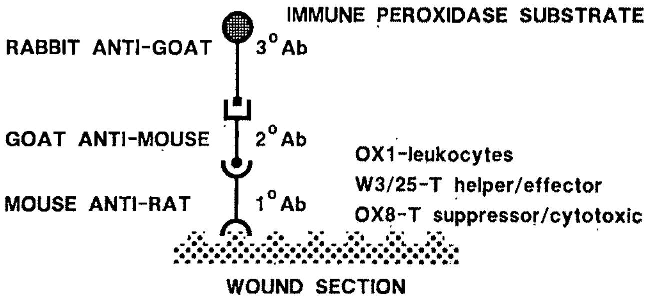


FIG. 1. Diagram of the immunohistochemical staining method used for the identification of antigens on the surface of wound cells by the use of monoclonal antibodies. Three reagents are used: (1) primary antibody, (2) second antibody capable of binding to the first, and (3) biotinylated third antibody. This can then form a biotin–avidin peroxidase complex.

The rats were killed at 5, 7, or 10 days after wounding. A segment of the healing wound was excised and frozen in isopentane cooled to −150 C with liquid nitrogen. Sponge granulomas were cleared of surrounding connective tissue and similarly frozen. Wound blocks and sponges were cut in a cryostat at −20 C. Serial sections were stained using an Avitin–Biotin complex.[7] Briefly, sections were incubated with mouse anti-rat primary monoclonal antibodies (Pel Freez, Rogers, AR) at a 1:50 dilution. The following monoclonal antibodies were used: OX1 against the rat leukocyte common antigen expressed by thymocytes, T and B lymphocytes, and macrophages; W3/25 against the helper/effector T lymphocyte subset; and OX8 against suppressor/cytotoxic T lymphocytes.[8] Sections were then treated with a 1:200 dilution of goat anti-mouse IgG antibody (Calbiochem, San Diego, CA), a 1:800 dilution of tertiary biotinylated rabbit anti-goat IgG antibody (Vector Laboratories, Burlingame, CA), and the Avitin-Biotin immune peroxidase complex (Vector Laboratories, Burlingame, CA).

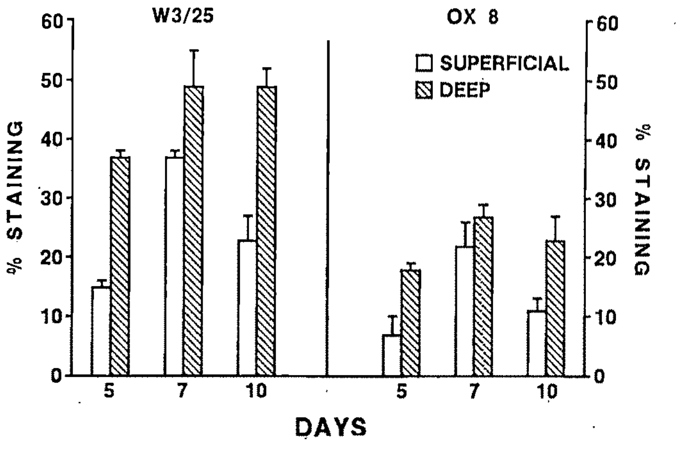


FIG. 2. Mean percentage of mononuclear wound cells stained with W3/25 or OX8 in the superficial and deep portions of the wound.

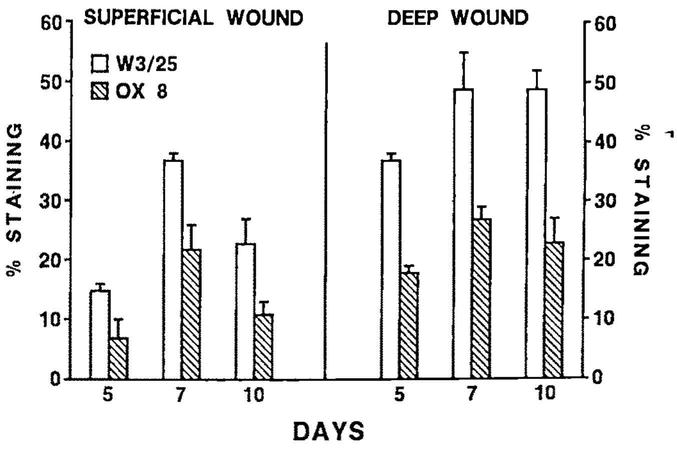


FIG. 3. Mean percentage of mononuclear wound cells stained with W3/25 or OX8 comparing the superficial and deep aspects of the wound.

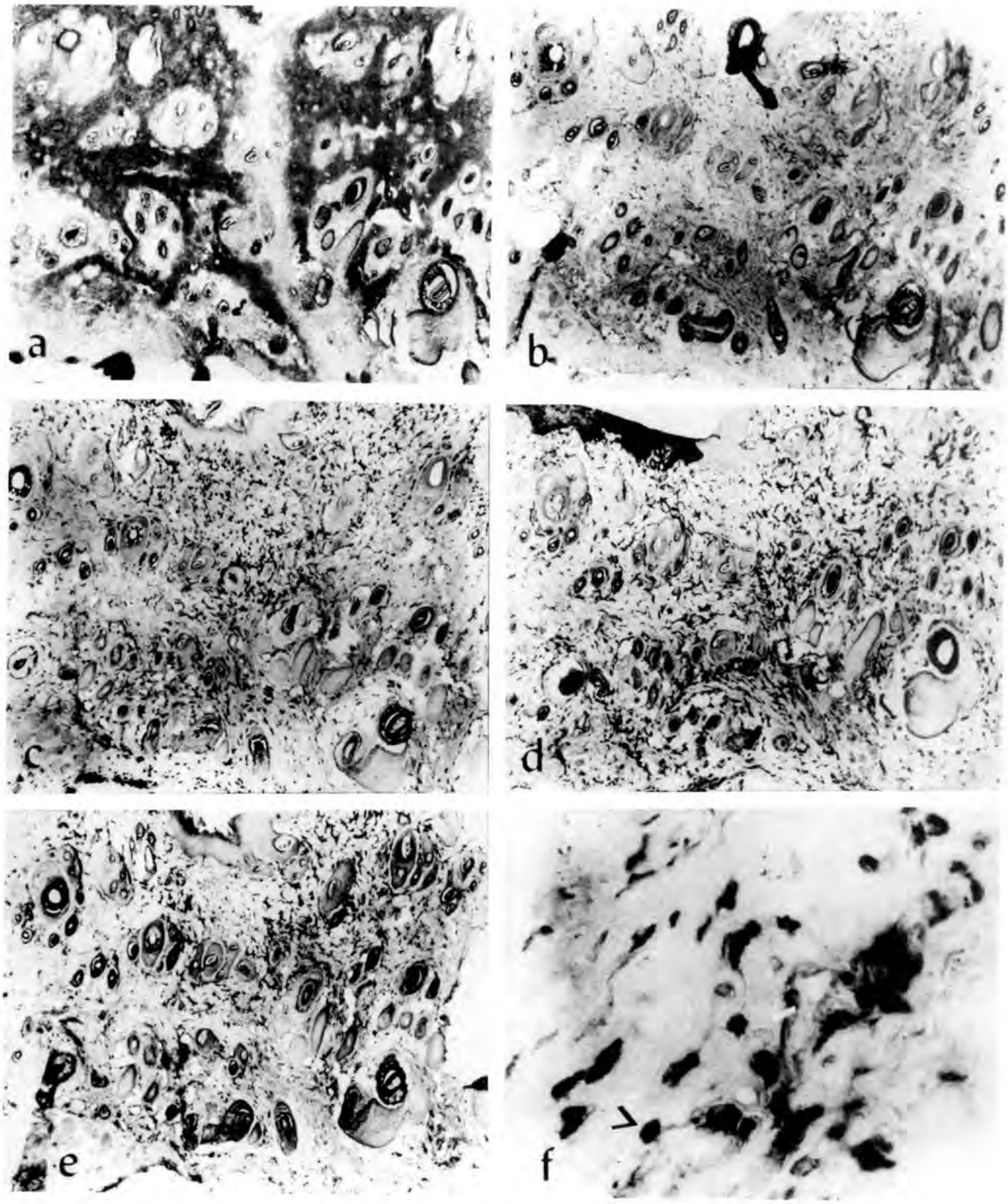
All incubations were for 30 minutes at room temperature in a humidified atmosphere. Figure 1 is a schematic representation of the staining technique used. Control sections received the same treatment except for the primary monoclonal antibody.

Sections stained with hematoxylin and eosin were studied to identify the wound or the location of cells in the sponge matrix. The mononuclear cell infiltrate of 5-, 7-, and 10-day-old wounds was ranked blindly using the OX1 stains. Cells stained with monoclonal antibody were counted in two areas of the wound: the superficial wound, down to and including the papillary dermis, and the deep wound, the reticular dermis. This division was made arbitrarily as it best reflected the areas of highest cellular infiltration. Cellular staining was quantitated in a blind fashion as follows: the section stained with OX1 that marks all leukocytes was counted. This allowed localization of the mononuclear wound cell populations to be counted in the subsequent serial sections (stained with the W3/25 and OX8 monoclonal antibodies). The exact number of cells counted was dependent on the overall mononuclear cell infiltrate of the wound or sponge. Between 100 and 300 round cells were counted in each area of the wound and the percentage of positivity by stained cells was determined. Likewise, 100–300 round cells were counted in each sponge section and the percentage of positive cells was determined.

Each data point reported in the study represents the mean of six separate wounds. The Mann-Whitney test was used to rank blindly the mononuclear cell infiltrate using the OX1 antibody.

Results

Five-day wounds had a significantly heavier mononuclear cell infiltration than 10-day wounds in the deep



FIGS. 4A–F. Composite of serial sections of a segment of a 7-day healing wound. *B–F.* Nuclei were counterstained with polychrome methylene blue. *A.* Hematoxylin-eosin stain of the healing wound. *B.* Negative control. Section stained using the biotin–avidin peroxidase technique excluding the primary monoclonal antibody. *C.* OX1. Section stained with primary monoclonal antibody against all leukocytes. Stained cells can be seen in all regions of the wound. *D.* W3/25. Staining is more marked in the deep rather than the superficial aspect of the wound. *E.* OX8. Fewer cells are stained compared with *D. F.* High power of W3/25. Note the discrete membrane staining (black arrow) *versus* unstained cells (white arrow).

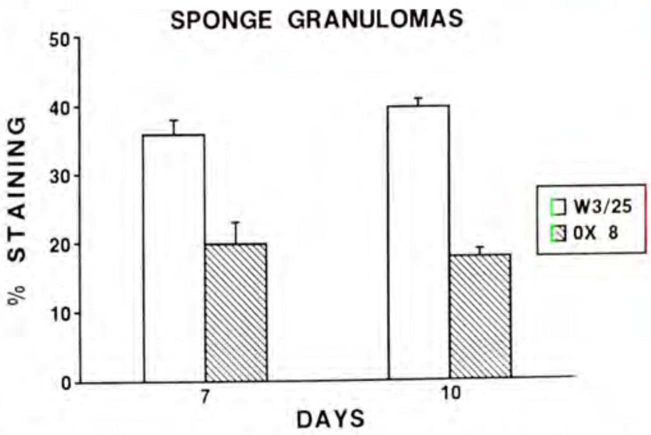


FIG. 5. Mean percentage of mononuclear wound cells stained with W3/25 and OX8 in the sponge matrix at 7 and 10 days.

portion ($p < 0.05$). This was also noted in the superficial section, although not as severe ($p < 0.10$). For 5-, 7-, and 10-day wounds (Fig. 2), lymphocytes labeled with W3/25 predominated over cells bearing the OX8 marker in approximately 2:1 ratios of the mean percentage positive cells in the superficial portions of the wound. There were twice as many W3/25 and OX8 labeled cells in the deep aspect of the wound as in the superficial portion at day 5 (W3/25, 37:15; OX8, 18:7) and day 10 (W3/25, 49:23; OX8 23:11). However, at day 7 there was a peak in W3/25 and OX8 labeled T lymphocytes in the superficial area, whereas the lymphocyte population in the reticular dermis (the deep portion) remained constant (Fig. 3). Figure 4 is an example of a 7-day wound. This is a composite picture showing serial sections of a 7-day healing wound stained with hematoxylin and eosin, monoclonal antibodies and a negative control.

T cells bearing the W3/25 and OX8 markers in the 7- and 10-day sponges were present at the same approximate 2:1 ratio as seen in the wound strips (Fig. 5). In the 5-day sponge, the lymphocytic infiltrate was insufficient to count.

Discussion

This experiment was designed to assess morphologically the migration of T lymphocyte subsets into surgical wounds. We also hoped to demonstrate that lymphocytes migrate to the implanted sponges in the same proportions as they do into the wounds. Were this the case, it would support the hypothesis that cells and fluid obtained from subcutaneously implanted sponges are representative of the cellular infiltrate into the wound itself.

T lymphocyte subsets positive for the W3/25 (helper/effector) and OX8 (suppressor/cytotoxic) markers were found to migrate to the superficial and deep portions of the wound in a 2:1 ratio. These ratios are similar to those reported in rat lymph nodes (1.7–2.3:1),[8,9] but lower than the ratio found in rat peripheral blood lymphocytes (4.2:1).[10] Wound lymphocyte migration is a dynamic process as populations of both W3/25- and OX8-positive T lymphocytes peak in the superficial area of the 7-day-old wound. This is similar to previous data that examined the dynamics of wound lymphocyte infiltration[1]; that study, however, did not study T lymphocyte subpopulations. Lymphocyte subsets infiltrate the implanted sponges in the same 2:1 ratio as seen in the wound, suggesting that the sponge granuloma cellular infiltrate reflects the cellular dynamics of the wound.

The role of lymphocyte participation in the healing process is not clear. Earlier work[6] suggested that wounds of rats depleted of lymphocytes healed dorsal wounds normally. However, we have found that alterations in the host's systemic immune responses influence wound healing. Treatment of rats with immunosuppressive doses of cyclosporin A (which has been shown to decrease the normal T helper/T suppressor ratios)[11] impairs wound healing.[5] Further, adult thymectomy, which abrogates the induction of suppressor T cells, enhances wound healing.[4] *In vitro* evidence suggests that lymphocytes can regulate fibroblast replication and collagen protein synthesis.[2,12] Both stimulated and unstimulated lymphocytes secrete soluble factors, lymphokines, that are reported to either inhibit or enhance fibroplasia.[12] However, the role these factors may play in *in vivo* wound healing remains to be elucidated.

More recently, work from our laboratory has demonstrated that *in vivo* depletion of T lymphocytes impairs wound breaking strength and collagen synthesis in a mouse wound healing model (unpublished data).

The current experiments demonstrate that lymphocytic infiltration of healing wounds is a dynamic process that peaks at 7 days after wounding. Although the morphologic methodology used herein does not allow for direct evaluation of lymphocyte-fibroblast interaction, it may be useful in studying whether the detrimental effect of lympholytic agents such as steroids or chemotherapeutic agents on wound healing is mediated by alterations in wound lymphocyte migration.

Addendum

Since carrying out these studies, a paper has been published using a similar technique to study the appearance of W3/13-positive lymphocytes in healing femoral fractures in rats.[13]

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Human Liver Regeneration after Major Hepatic Resection

A Study of Normal Liver and Livers with Chronic Hepatitis and Cirrhosis

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The regenerative process was evaluated in terms of liver size, function, and histology in 28 adults who had major hepatic resection: hepatocellular carcinoma (HCC) in 21, secondary liver cancer from colorectum in four, carcinoma of the gallbladder in one, Klatskin tumor in one, and Caroli's disease in one. There were 22 men and six women. Ages ranged from 17 to 74 years with a mean age of 56.7. All patients with HCC had underlying liver disease: liver cirrhosis in 14 and chronic hepatitis in seven. Extended right lobectomy was done on 10 patients, right lobectomy on 16 patients, and left lobectomy on two patients. The residual liver size was serially estimated with computed tomography (CT) in 15 patients: six with normal liver, five with chronic hepatitis, and four with cirrhosis. A complete restoration of the residual liver size was found within 3 months in 3 and 6 months, respectively, in two patients with normal livers. The liver was enlarged in all patients with the parenchymal diseases but obviously more slowly compared with normal liver. Liver functions were restored normally within 2–3 weeks in patients with normal livers, but hyperbilirubinemia persisted longer in those with chronic hepatitis and cirrhosis. A continuous rise of bilirubin was an ominous sign of liver failure and subsequent death, which occurred in five patients with cirrhosis. Serum alpha-fetoprotein did not rise in accordance with the regeneration. Histologically, evidence of active regeneration with increased mitotic activity was found at 10 and 35 days in those patients with normal livers. Mitosis was not seen in a specimen taken at 7 days. Enlarged cuboidal hepatocytes and cells with basophilic cytoplasm or two nuclei were observed more or less in all specimens. The livers with cirrhosis or hepatitis also showed histologic evidence of regeneration during the first 2 months but substantially less compared with normal liver, which was well supported by the volumetric study of the liver remnants with CT.

THE LIVER EXHIBITS a remarkable regenerative capacity after major resection provided it is normal. It is commonly assumed that a normal liver tolerates a 70–80% resection safely[1–6] but several authors[7,8] have reported a formidable resection as large as 90% with subsequent regeneration of the liver remnant. On the other hand, it is well known that cirrhotic livers are less able to regenerate and accordingly that major resection is contraindicated in the presence of liver cirrhosis.[3,6] We have recently shown, however, that some of the patients with cirrhosis can tolerate extensive hepatic resection, and therefore that it is wiser to select candidates for major resection from the patients with cirrhosis by quantitative evaluation of hepatic reserve in each case.[9,10]

To date, there have been several clinical works in which the regenerative process of liver remnants was radiologically followed up using liver scan[2,3,6–8,11] or angiography[11–14] or checked by second-look operations.[1,12] These methods, however, do not provide exact estimation of the size of liver remnants. We have investigated the exact volume of the liver after major hepatic resection using computed tomography (CT) in patients with normal liver and livers with chronic hepatitis and cirrhosis. At the same time, the regenerative process was evaluated by conventional function tests and histologic studies.

Materials and Methods

From January 1980 to December 1985, the regenerative process of human liver was evaluated in 28 adult patients who had had major hepatic resection. There were 22 men and six women. Ages ranged from 17 to 74 years with a mean age of 56.7 ± 13.6 years (±SD). Hepatic resections were done for the treatment of hepatocellular carcinoma (HCC) in 21 patients who had either liver cirrhosis (14 patients) or chronic hepatitis (7 patients). Among seven patients with normal liver, four had secondary liver cancer from the colorectum, one

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had carcinoma of the gallbladder, and one had cholangiocarcinoma of the liver hilus (Klatskin tumor). The last patient had Caroli's disease of the right hepatic lobe. Extended right lobectomy was done on 10 patients, right lobectomy was done on 16 patients, and left lobectomy was done on two patients.

Measurement of Liver Volume

Volume estimations of the liver remnant were serially performed by CT in 15 patients: six with normal liver, five with chronic hepatitis, and four with liver cirrhosis. As control, the size of normal liver was estimated in six men and six women whose ages ranged from 20 to 70 years. Serial transverse scans of the liver were taken with a GE CT/T 8800 (General Electric Medical Systems, Milwaukee, WI) at 1-cm intervals. All slices of the liver were traced on a tracing paper that was known to produce an exact direct proportion between weight and area. The paper weight of all the hepatic areas was measured with a microestimation balance and the total area of them was gained from the proportional line. The actual volume of the liver was obtained by dividing the data by reduction rate (0.0676).

Liver Function Tests

Conventional liver tests were determined on the first, third, and seventh postoperative days, and at weekly intervals thereafter.

Serum alpha-Fetoprotein Levels

Serum alpha-fetoprotein (AFP) levels were serially estimated in seven patients with normal liver and in five patients with chronic hepatitis up to 15 weeks after hepatic resection. A radioimmunoassay method was used for the measurements.

Histologic Studies

Hepatic specimens were taken by needle biopsy with a Vim-Silverman needle or at the time of relaparotomy or autopsy 7–240 days after operation in 13 patients: five with normal liver, four with chronic hepatitis, and four with liver cirrhosis. The specimens were stained with hematoxylin and eosine, and were evaluated in terms of regeneration of the liver remnant.

Results

Size of the Liver Remnant

The normal liver size was 1086 ± 88 cm^3 in males and 1006 ± 52 cm^3 in females (mean ± SE). Serial changes in the remnant liver size are shown in Figures 1–3. The background of the patients in each category is shown in Table 1. The initial values indicate the sizes of the entire livers with tumors. The size immediately after hepatic resection was calculated by the extent of the resection. Extended right lobectomy was calculated as 80% among

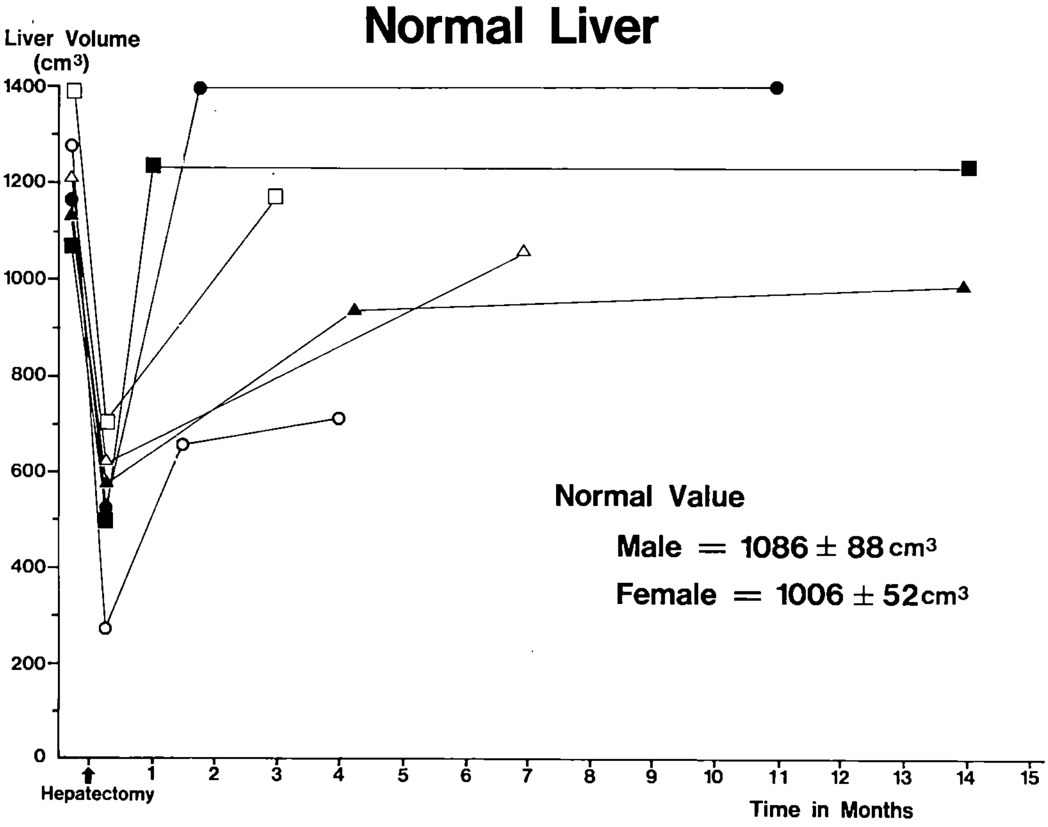


FIG. 1. Changes in liver volume estimated with CT after major hepatic resection in patients with normal livers.

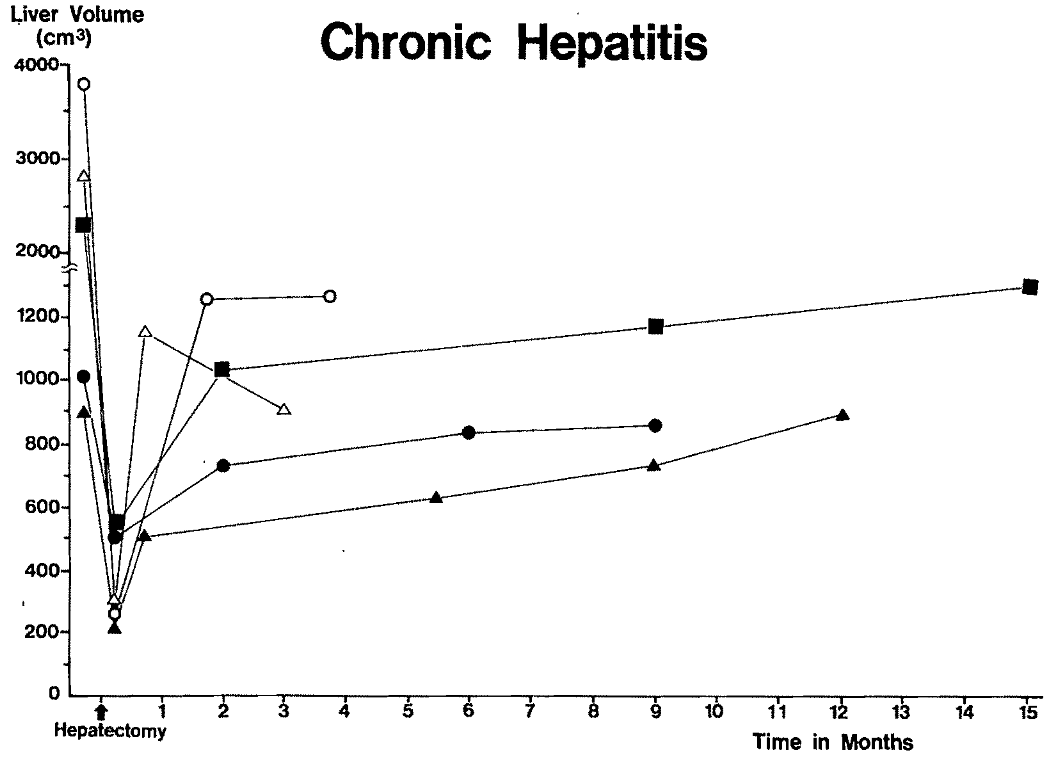


FIG. 2. Changes in liver volume estimated with CT after major hepatic resection in patients with chronic hepatitis.

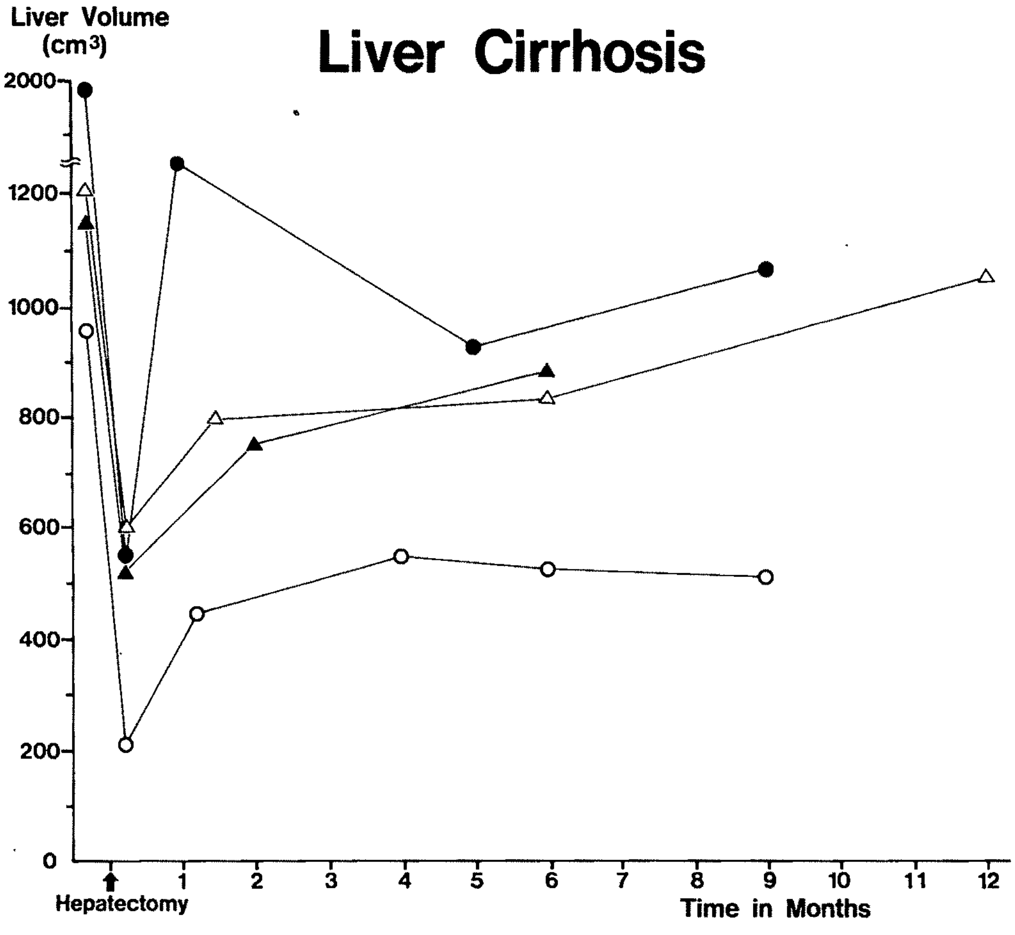


FIG. 3. Changes in liver volume estimated with CT after major hepatic resection in patients with liver cirrhosis.

TABLE 1. *Clinical Data of 15 Patients in whom Liver Size was Serially Estimated by CT*

Group/Case No.	Age	Sex	Disease	Type of Liver Disease	Operation	Resected Liver Weight (g)
Normal liver						
1	45	F	Caroli's disease	None	RL	580
2	72	F	Gallbladder cancer	None	ERL	750
3	53	F	SLC	None	RL	650
4	66	M	SLC	None	RL	560
5	63	F	SLC	None	RL	540
6	20	M	Klatskin tumor	Obstructive jaundice	RL	785
Chronic hepatitis						
1	71	M	HCC	Inactive	RL	550
2	57	M	HCC	Active	ERL	2480
3	51	F	HCC	Active	ERL	915
4	17	M	HCC	Inactive	ERL	1300
5	70	M	HCC	Inactive	RL	1060
Liver cirrhosis						
1	53	M	HCC	Macronodular	RL	1000
2	66	M	HCC	Micronodular	ERL	540
3	57	M	HCC	Macronodular	RL	500
4	57	M	HCC	Micronodular	RL	400

SLC = Secondary liver cancer from colorectum.
HCC = Hepatocellular carcinoma.
RL = right lobectomy.
ERL = extended right lobectomy.

resection, right lobectomy as 60%, and left lobectomy as 40%. Among six patients with normal liver, five had a complete restoration of liver volume within 7 months (Fig. 1 and Fig. 4). Three of them had a larger liver than normal within 3 months. In an oldest patient (Case 2) who had carcinomatous peritonitis occurring soon after operation, the liver regeneration was substantially insufficient. In the presence of chronic hepatitis, two patients had a rapid regeneration of the liver remnant (Fig. 2 and Fig. 5). The liver grew more gradually in two patients and size never exceeded the normal liver volume up to 9–12 months after operation. In the youngest patient, the liver remnant was larger than normal only 3 weeks after operation but it regressed 3 months later probably due to extensive intra-arterial chemotherapy with 5-fluorouracil, doxorubicin, and mitomycin C. Among four patients with liver cirrhosis, the size of liver remnants returned nearly to normal 9–12 months after operation in two patients. It was restored to 879 cm^3 at 6 months in one patient (Case 3) (Fig. 3 and Fig. 6). One patient (Case 2) had gradual liver growth after extended right lobectomy for 4 months but no enlargement was found thereafter. The liver size in this patient remains at approximately 500 cm^3 but he has been leading a normal life.

Liver Functions

Aspartate aminotransferase (AST) activities were substantially elevated in all patients on the first postoperative day but returned to the preoperative levels within 2 weeks in most patients. The peak of the enzymatic activity was significantly lower in the patients with cirrhosis than in the noncirrhotic patients (Fig. 7). Serum bilirubin levels rose immediately after operation in most patients. They returned to normal within 2 weeks in pa-

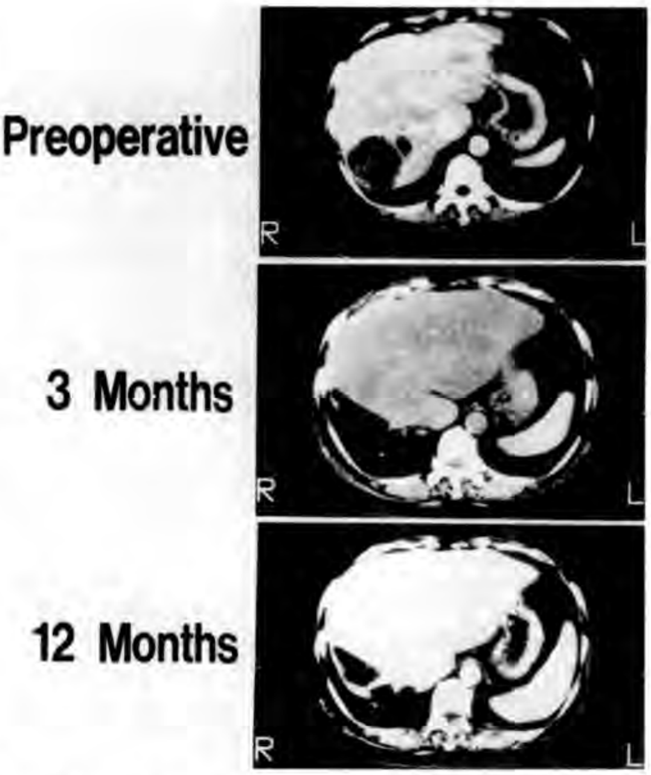


FIG. 4. Serial CT scans after right lobectomy in a patient with normal liver (Case 3).

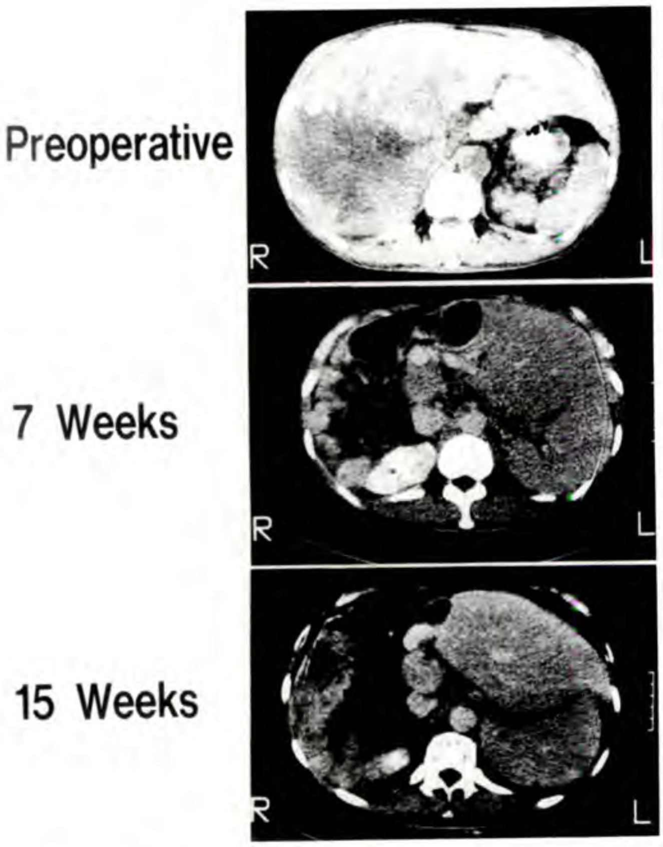


FIG. 5. Serial CT scans after extended right lobectomy in a patient with chronic hepatitis (Case 2).

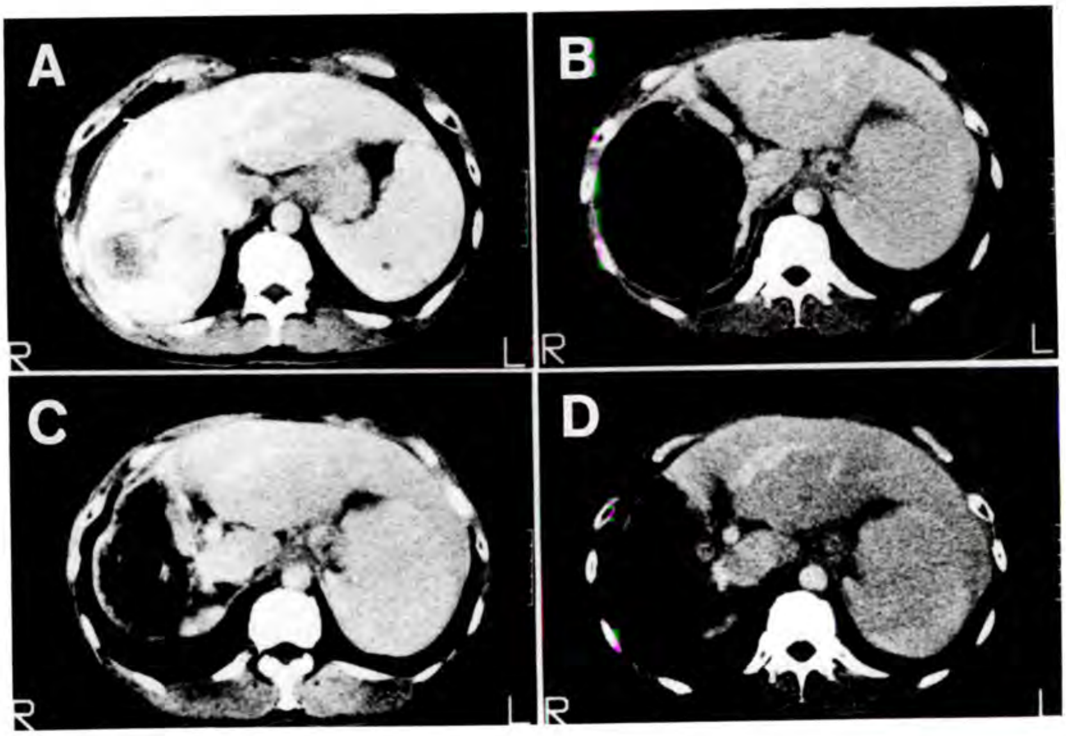
tients with normal livers but this retarded in the patients with chronic hepatitis. This tendency was more intense in the patients with cirrhosis and the five patients who died of liver failure had a progressive elevation of bilirubin levels (Fig. 8). Serum protein levels rarely fell below 6.0 g/100 mL in those patients with normal livers. On the contrary, patients with cirrhosis showed a profound drop despite extensive substitution, and this trend was most severe in the patients who died of liver failure (Fig. 9). Changes in total cholesterol levels were similar to those in total protein (Fig. 10).

Serum AFP

Serum AFP concentrations were fluctuated within normal ranges in all patients who had normal livers. In patients with chronic hepatitis, AFP was never elevated in accordance with regeneration of the liver remnant. One exception was a patient in whom cholestatic hepatitis occurred 5 weeks after operation. Serum AFP was transiently elevated during the recovery phase of the hepatitis in this patient (Fig. 11).

Histologic Findings of Liver Remnants

Normal liver. The cytoplasm of hepatocytes at the periportal zone became basophilic, and cellular enlargement and sinusoidal dilatation of slight degree were observed at 7 days. Mitotic figures were not seen although



FIGS. 6A–D. Serial CT scans after right lobectomy in a patient with liver cirrhosis (Case 4). *A.* Preoperative CT scan. *B.* 1.5 months. *C.* 6 months. *D.* 12 months.

binuclear cells were sporadically observed. Steatosis of moderate degree was found. The number of basophilic hepatocytes increased at 10 days. There were many enlarged cuboidal hepatocytes. Cells with mitosis and two nuclei were frequently seen. The sinusoids were dilated but liver steatosis was very slight (Fig. 12). Similar findings were observed in the specimen taken 35 days after operation. Almost normal histologic configurations were found in the specimens obtained 4 and 5 months after operation.

Chronic hepatitis. In the liver taken 30 days after extended right lobectomy, there were a few hepatocytes with basophilic cytoplasm and enlarged cuboidal cells. Binuclear cells were remarkably found but there were no mitoses. Neither sinusoidal dilatation nor liver steatosis was observed (Fig. 13). These findings were more slight in the specimens taken at 60 days, 7 months, and 8 months.

Liver cirrhosis. In the liver taken 13 days after right lobectomy, more basophilic liver cells were found compared with before operation. Although binuclear cells were sporadically seen, there were no hepatocytes with mitosis. Few enlarged cuboidal cells were noted. Steatosis or sinusoidal dilatation was not remarkable. Similar findings were observed in the specimen taken at 33 days. In a patient who died of liver failure 15 days after operation, necrosis of centrizonal hepatocytes was diffusely found. No regenerative reaction was observed. In another patient who died of chronic liver failure at 56 days, liver cells were preserved rather well. There were many sludges of bile pigments in the bile ductules. Few findings suggesting liver regeneration were observed (Fig. 14).

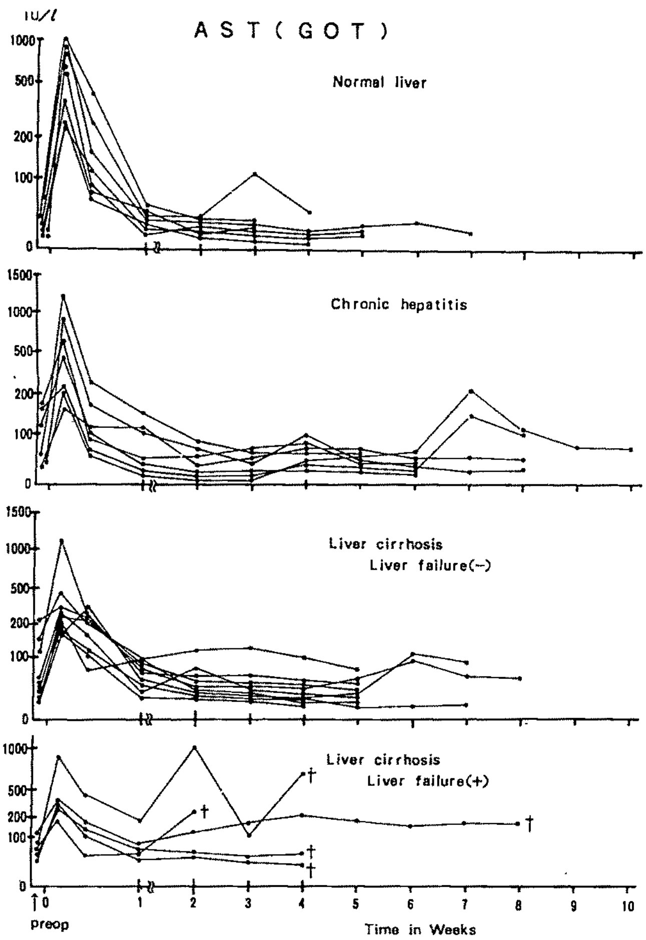


FIG. 7. Changes in serum aspartate aminotransferase (AST) activities after major hepatic resection.

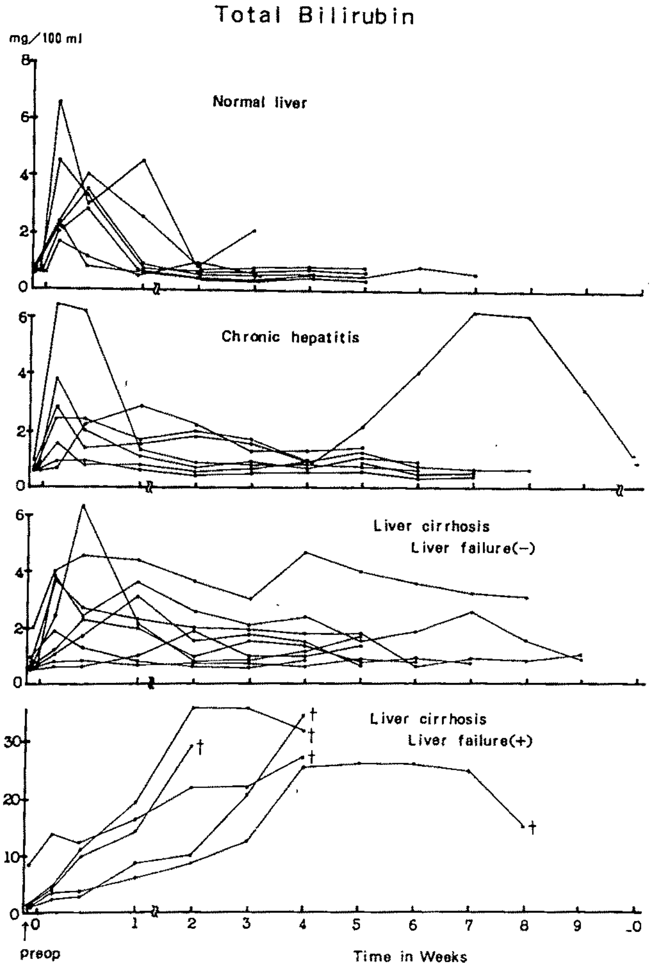


FIG. 8. Changes in serum bilirubin levels after major hepatic resection.

Discussion

Details on human liver regeneration are difficult to obtain unlike experimental animals for apparent reasons. Pack et al.[1] in 1962, confirmed a rapid regeneration of the residual liver during relaparotomy in four patients who had undergone major hepatectomy for the

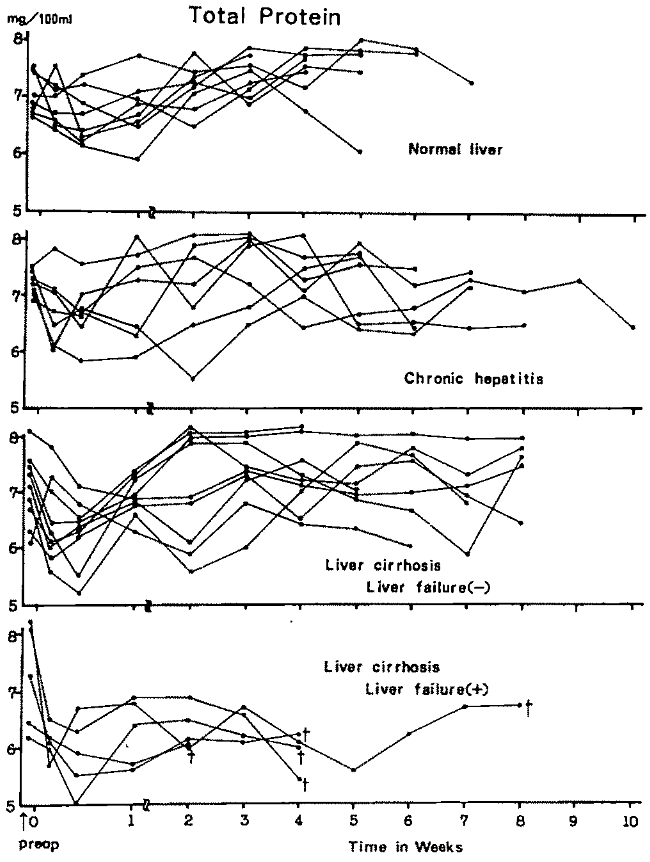


FIG. 9. Changes in serum protein levels after major hepatic resection.

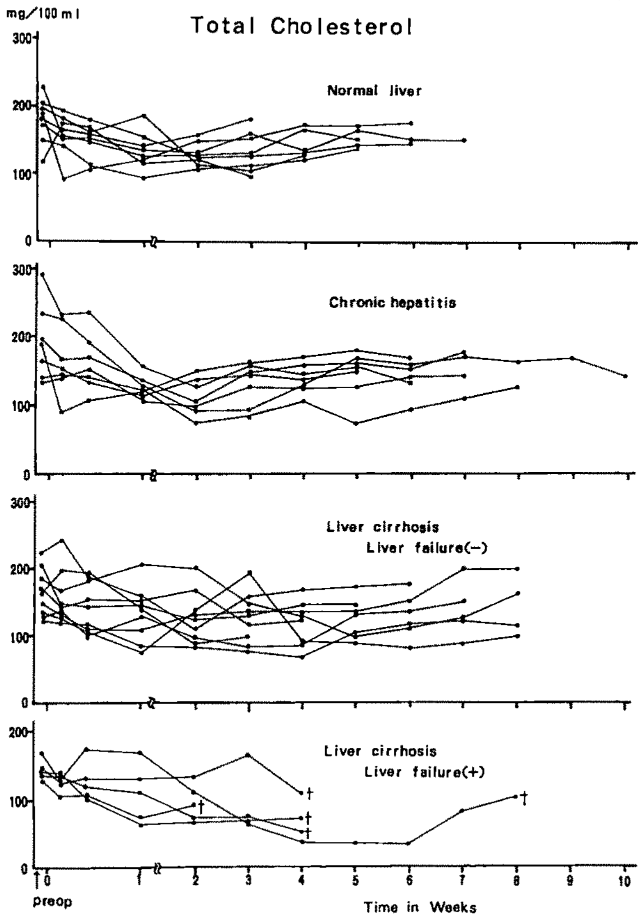


FIG. 10. Changes in serum cholesterol levels after major hepatic resection.

treatment of cancer. Thereafter, several investigations on regeneration of normal human liver were reported with the aids of liver scan[2,3,6–8,11] and angiography.[11–14] The general conclusion from those studies was that a normal liver regains its original size within 6 months after extensive hepatic resection.[2,4,7,12]

In the current study using CT, three patients with normal liver showed a complete restoration of the residual liver size within 3 months. Slower and incomplete regeneration was found in only one patient who had carcinomatous peritonitis immediately after the operation. In the patients with chronic hepatitis and liver cirrhosis, the remnant liver was enlarged but obviously more slowly compared with normal liver. Among four patients with chronic hepatitis, only one had a rapid regeneration. Three patients had on-going regeneration 9–15 months after operation. Two patients with cirrhosis had a nearly normal liver volume at 9 and 12 months after operation, respectively. In one cirrhotic patient with extended right lobectomy, the residual liver has grown up to only one half of the normal size but he has been leading a normal life.

Thus, a normal liver seems to regenerate much faster than previously assumed. Cirrhotic livers or livers with chronic hepatitis, on the other hand, enlarge more

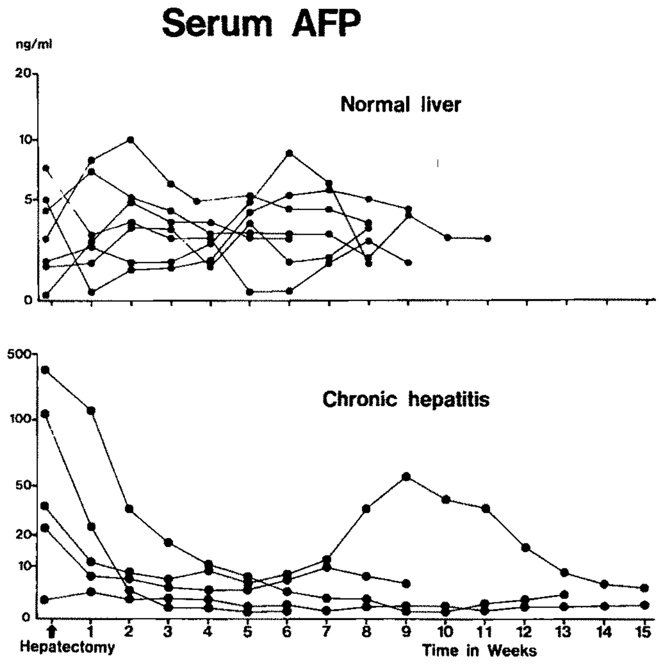


FIG. 11. Changes in serum AFP levels after major hepatic resection (normal range: less than 20 ng/mL).

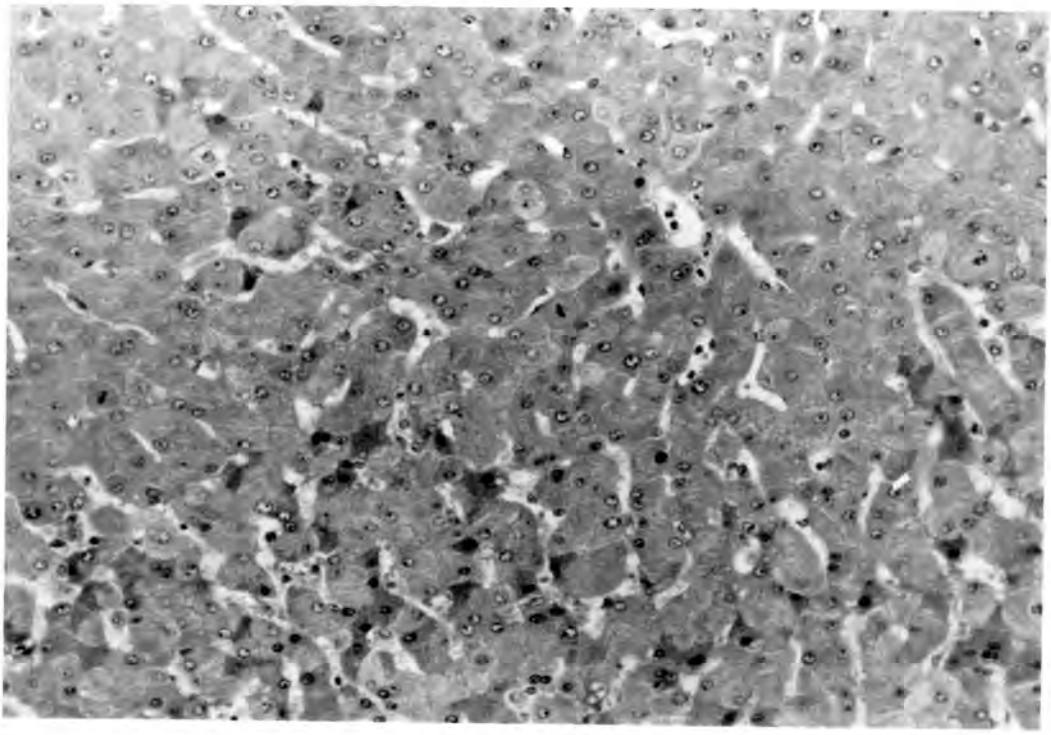


FIG. 12. Histology of the residual liver taken 10 days after right lobectomy in a patient with normal liver (hematoxylin and eosin, original magnification ×50).

slowly, but complete restoration of the residual liver is possible in some patients with these parenchymal diseases. Lin and his associates[3,6] claim that a cirrhotic liver cannot regenerate and, therefore, that major hepatic resection is contraindicated in the presence of cirrhosis of the liver. Our current study casts a question to this. Probably the prognosis of patients with cirrhosis who have major hepatic resection depends on the extent of the cirrhosis. In fact, Kohno et al.[15] have found that the prognosis of dogs with experimentally induced cirrhosis was well reflected by the extent of the cirrhosis. The "all or nothing theory" that cirrhotic livers do not tolerate a

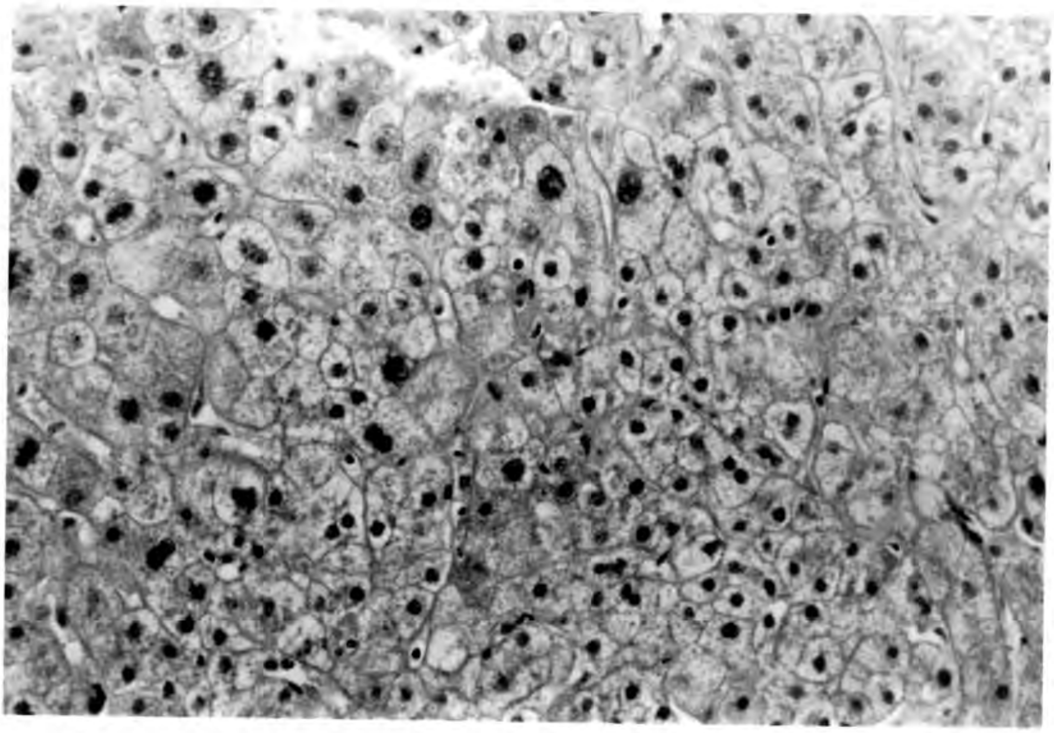


FIG. 13. Histology of the residual liver taken 30 days after extended right lobectomy in a patient with chronic hepatitis (hematoxylin and eosin, original magnification ×297).

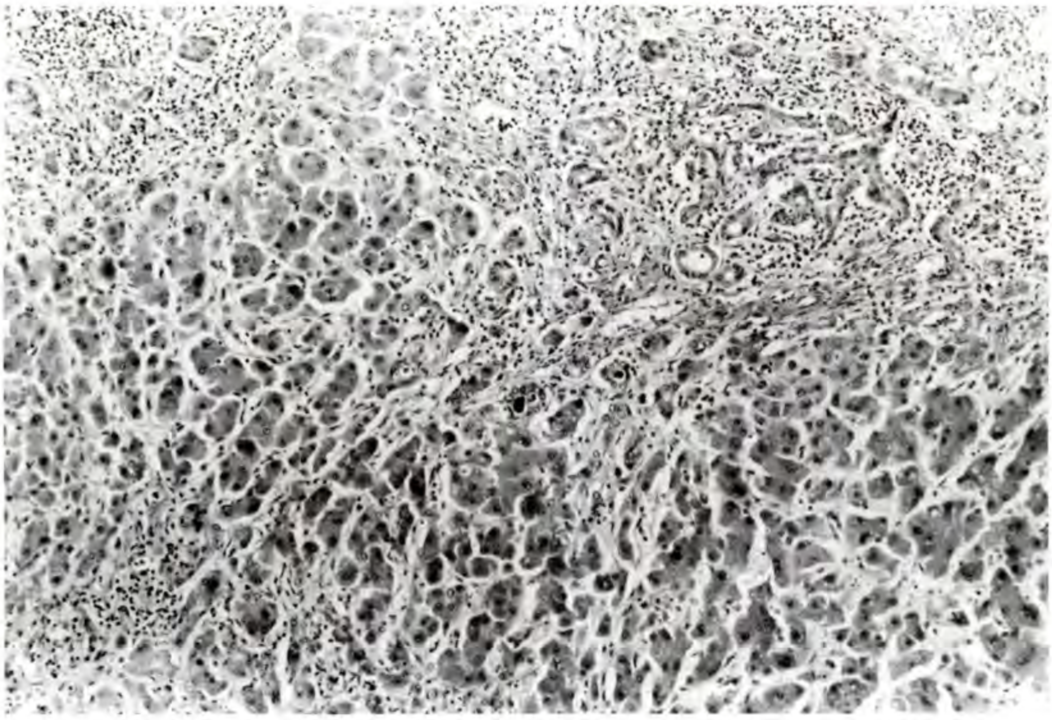


FIG. 14. Histology of the residual liver at autopsy 56 days after right lobectomy in a patient with liver cirrhosis who died of hepatic failure (hematoxylin and eosin, original magnification ×25).

major resection seems to be invalid. We should select candidates for such resections by a quantitative, not qualitative, evaluation, although it is difficult how to do it.[9,10]

Postoperative liver functions were restored almost normally within 2–3 weeks in patients with normal livers. This correlates with the previous results.[2,3,5,16–18] However, hyperbilirubinemia of slight degree persisted longer in the patients with parenchymal disease. A steady rise of serum bilirubin was an ominous sign of hepatic failure in the patients with cirrhosis. None of the patients with chronic hepatitis, either active or inactive, had such a continuous elevation of bilirubin and subsequent hepatic failure.

It is well known that the peak of mitosis of hepatocytes occurs 24–28 hours in rats[19] and 4 days in dogs[20] after 70% hepatectomy. No data are available on this subject in human liver. Vajrabukka et al.[5] found histologic evidence of regenerative hyperplasia with increased mitotic activity within 3 days after partial hepatectomy. Lin et al.[6] also histologically observed regeneration of the normal residual liver 5–27 days after operation. In our patients with normal liver, mitoses were found at 10 and 35 days but not at 7 days. Enlarged cuboidal hepatocytes, cells with basophilic cytoplasm or two nuclei, and liver steatosis were observed more or less in all these specimens. The liver remnant was morphologically normal 4–5 months after operation. In light of this and previous studies,[5,6] it is likely that normal human liver starts to regenerate soon after partial hepatectomy and cellular proliferation continues for several weeks thereafter. The liver with cirrhosis or hepatitis also showed histologic evidence of regeneration but obviously less compared with normal liver, which was well supported by the volumetric study of liver remnants with CT.

Serum AFP was not a reliable indicator for liver regeneration after partial hepatectomy as previously suggested by Alpert and Feller[21] and ourselves.[22] Serum AFP was never elevated during the period of active regeneration of the liver remnant in patients with normal livers or chronic hepatitis. It rose transiently during the recovery phase of postoperative hepatitis in one patient who had chronic hepatitis initially and had undergone extended right lobectomy. Therefore, we are reluctant to assume that the elevation of serum AFP that is occasionally seen in chronic liver disease is reflected by regeneration of the liver.

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Regional Therapy in the Management of Intrahepatic Recurrence after Surgery for Hepatoma

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The significance of regional therapy against the intrahepatic recurrence for hepatocellular carcinoma (HCC) was evaluated. During the past 6 years, 101 patients who had radical operations for HCC (liver cirrhosis, 75%; chronic hepatitis, 22%) were followed. Forty-seven patients (47%) had recurrences; the liver was the site of first recurrence in 43 patients and distant site recurrence in four patients. In the patients where the liver was the recurrent site, 33 patients (77%) received regional therapies for an aggregate total of 60 times. Transcatheter arterial chemoembolization was chosen as the first preferred therapy against recurrence in the liver in 30 of 33 patients (91%). Postrecurrence survival of the patients treated with regional therapy was significantly better than disease-free survival ($p < 0.001$). Disease-free survival after surgery, postrecurrence survival, and postsurgery survival were compared in the patients treated with regional therapy and untreated patients. Fifty per cent survival after recurrence of the treated patients was 27 months, and that of the untreated patients was 3 months. Postrecurrence survival ($p < 0.001$) and postsurgery survival ($p < 0.01$) of the treated patients were significantly better than those of the untreated patients. To obtain successful long-term survival after surgery for the cirrhotic patients with HCC, it is necessary to repeat active regional therapies against the recurrent liver.

THE PATIENTS WHO HAD hepatocellular carcinoma (HCC) with liver cirrhosis were excluded from indications for hepatic resection in Western countries because of poor prognosis.[1,2] Since, however, HCC in Asian countries, including Japan, is associated with cirrhosis in high frequency,[3,4] the cirrhotic patients with HCC cannot be eliminated from the subjects of the treatment for clinicians who practice in areas where prevalence of the disease is high. In recent years, the remarkable progress in imaging modalities, such as ultrasonography (US), computed tomography (CT), and the monitoring of serum α-fetoprotein (AFP) levels in high-risk patients, has made it possible to detect small HCC at an early stage. Consequently, the surgeons have been able to resect HCC successfully at a relatively early stage in some patients. Moreover, the improvement of the assessment of resectability,[5,6] the concept of limited operation,[7] and the subsegmental or partial resection using intraoperative US[8,9] have produced high resectability and low operative mortality rates. However, the long-term survivals after surgery reported by the surgeons in the Asian countries are not yet satisfactory. Tsuzuki et al.[10] reported that the 3-year actual survival rate was 31%, Okamoto et al.[11] reported that the 3- and 5-year survival rates were 26.7% and 13.3%, respectively, and the recent report by Lee et al.[12] showed a 28% survival rate for 1400 days. One reason for these poor cure rates is believed to be related to the high recurrence rate in the liver remnant because the cirrhotic liver limits the extent of the hepatic resection.

During the past 6 years, we have carefully followed up on the patients who had surgical resection for HCC at the Center for Adult Diseases, Osaka, Japan. When recurrences were recognized in the liver, the active regional therapies were applied. In this study, the significance of the regional therapy against the intrahepatic recurrences for HCC is evaluated.

Patients and Methods

During the past 6 years ending in June 1986, 114 patients with HCC had radical hepatic resection at this center. Of the 114 patients, 13 had either operative or in-hospital death; therefore, the remaining 101 patients (89%) were studied. Surgery was defined to be radical in cases where all gross disease was removed, including a

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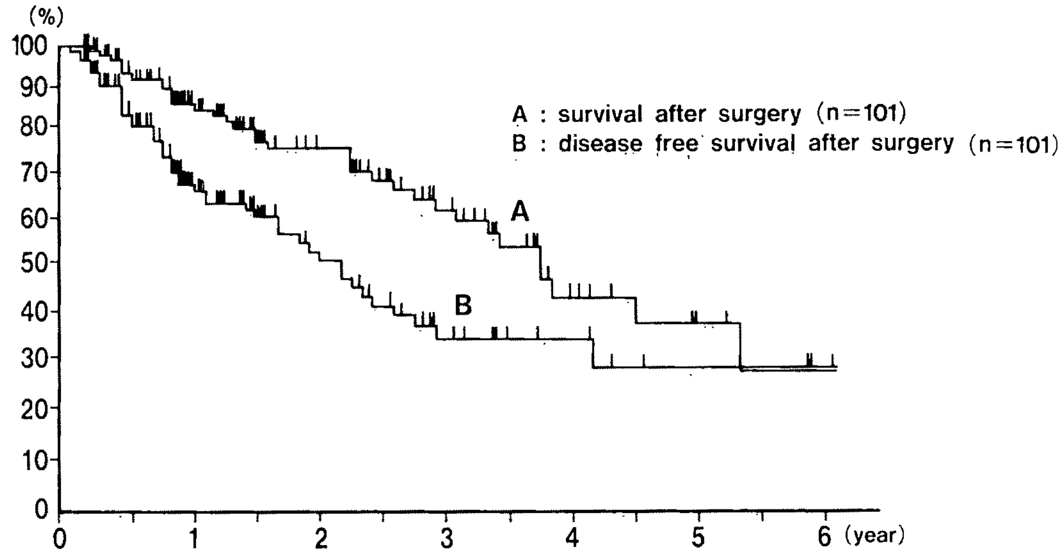


FIG. 1. Survival and disease-free survival after surgery in 101 patients who had the radical operation. A to B: $p < 0.01$.

disease-free resection margin. The 101 patients included 82 men (81%) and 19 women (19%), ranging in age from 35 to 75 years (mean: 58 years). Seventy-six patients (75%) had cirrhosis, 22 patients (22%) had chronic hepatitis, and three patients (3%) had normal parenchyma. Thirty-eight patients (38%) had partial hepatic resection, 26 patients (26%) had hepatic subsegmentectomy,[13] 24 patients (23%) had hepatic segmentectomy, and 13 patients (13%) had hepatic lobectomy or extended hepatic lobectomy. After resection, the patients were followed up every 1-3 months. AFP assays, liver function tests, liver US, and chest x-ray were routinely performed. When recurrences were suspected, the patients received liver CT and were readmitted to the hospital for hepatic angiography.

Statistical Analysis

Cumulative survival rates and curves were calculated using the Kaplan-Meier method. The generalized Wilcoxon test was used to compare the survival curves. The p values less than 0.05 were considered to be statistically significant.

Results

Recurrence and Survival

By the end of September 1986, 47 of 101 patients (47%) had recurrences. Twenty-nine patients with recurrence (62%) had recurrences within 1 year after surgery, nine patients (19%) had recurrence from 1 to 2 years after surgery, seven patients (15%) had recurrence from 2 to 3 years after surgery, and the remaining two patients had recurrence more than 3 years after surgery. Of the 47 patients, the liver was the site of first recurrence in 43 patients (91%), and four (4%) were found in distant sites. At this time, 69 patients (68%) were alive and 32 patients (32%) were dead. The 1-, 3-, and 5-year disease-free survival rates of the 101 patients were 70%, 36%, and 30%, respectively, and the 1-, 3-, and 5-year survival rates of these were 87%, 64%, and 40%, respectively (Fig. 1).

Tumor Size, Extent of Resection, and Disease-free Survival

To examine the influence of tumor size and the extent of resection on the recurrence, disease-free survivals after surgery with respect to these factors were calculated (Fig. 2 and Fig. 3). A statistically significant difference was found among the groups with the tumor size below 2 cm and the group with the tumor size exceeding 10 cm ($p < 0.05$). The 2-year disease-free survival rate of the group with the tumor size below 2 cm was significantly better than the other groups. There were no significant differences among the groups with the tumor size exceeding 2 cm (Fig. 2). On the other hand, the extent of resection did not influence disease-free survival (Fig. 3).

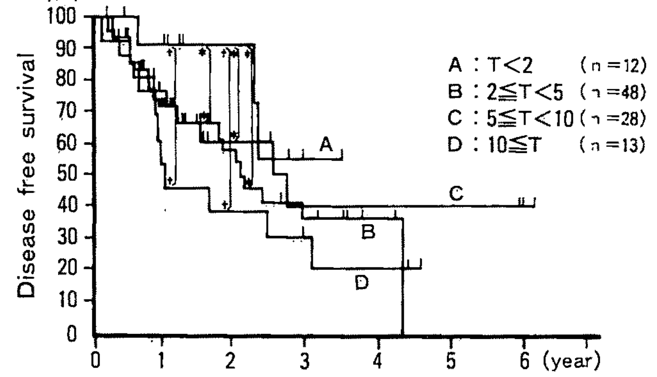


FIG. 2. Disease-free survival after surgery in tumor size. T: tumor size (cm). A to D: $p < 0.05$. $^{*}p < 0.05$, $^{\dagger}p < 0.01$, $^{\ddagger}p < 0.001$.

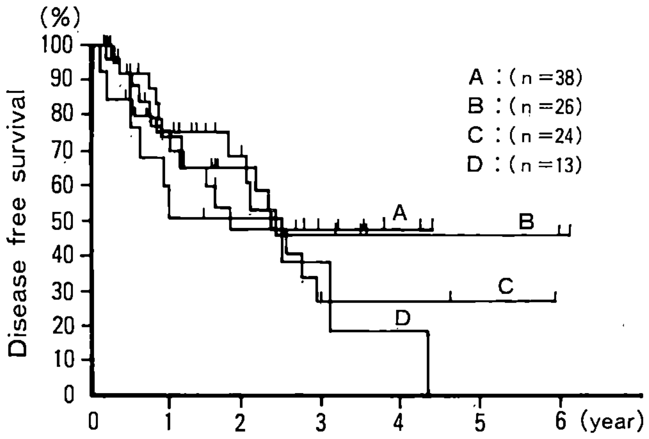


FIG. 3. Disease-free survival after surgery in extent of resection. A: partial hepatic resection, B: subsegmentectomy, C: segmentectomy, D: lobectomy or extended lobectomy.

Regional Therapy against the Intrahepatic Recurrence

In the 43 patients where the liver was the site of first recurrence, 33 patients (77%) received the regional therapies (Fig. 4 and Fig. 5) and the remaining 10 patients (23%) did not. Interventional angiographic technique was chosen as the first therapy against the recurrent disease in 30 of 33 patients (91%). As one of the transcatheter procedures, chemoembolization, *i.e.*, the combination of intra-arterial infusion of a chemotherapeutic agent and arterial embolization, was mainly performed under the following regimens: (1) by absorbable gelatin sponge cubes (Gelfoam®; Upjohn Company, Kalamazoo, MI) after arterial infusion of 40–60 mg of adriamycin (ADM); (2) after arterial infusion of 10–20 ml of ethiodized oil (Ethiodol®; Savage Laboratories, Melville, NY, Lipiodol®; Laboratoire Guerbet, Aulnay-sous-Bois, France) containing 40–60 mg of ADM; and (3) chemoembolization using a combination of 10–20 ml of ethiodized oil, 2 mg/kg of body weight of cisplatin (CDDP), and Gelfoam.[14] When the tumor emboli were recognized in the trunk or the first branch of the portal vein on the hepatic portogram, embolization with Gelfoam was not performed, and the anticancer agent alone, or the anticancer agent plus ethiodized oil, was injected through the hepatic artery. One patient had hepatic resection as a first therapy against the recurrence. Two patients had cannulation and/or ligation of the hepatic artery through surgery because the transcatheter approach was impossible. They received intra-arterial chemotherapy or chemoembolization *via* the cannulated tube. Subsequent to first therapy against recurrence, the patients were followed up again. When relapse was recognized, the regional therapies were repeated. As a rule, when the previous therapy was considered to be effective, the same regimen was adopted. If the previous therapy seemed to be ineffective or when the same therapy was impossible to repeat, one of the other therapies was chosen. One patient received the regional therapies five times after recurrence, two patients received them four times, nine patients received them three times, 15 patients received them twice, and the remaining patients received them once (Fig. 4 and Fig. 5).

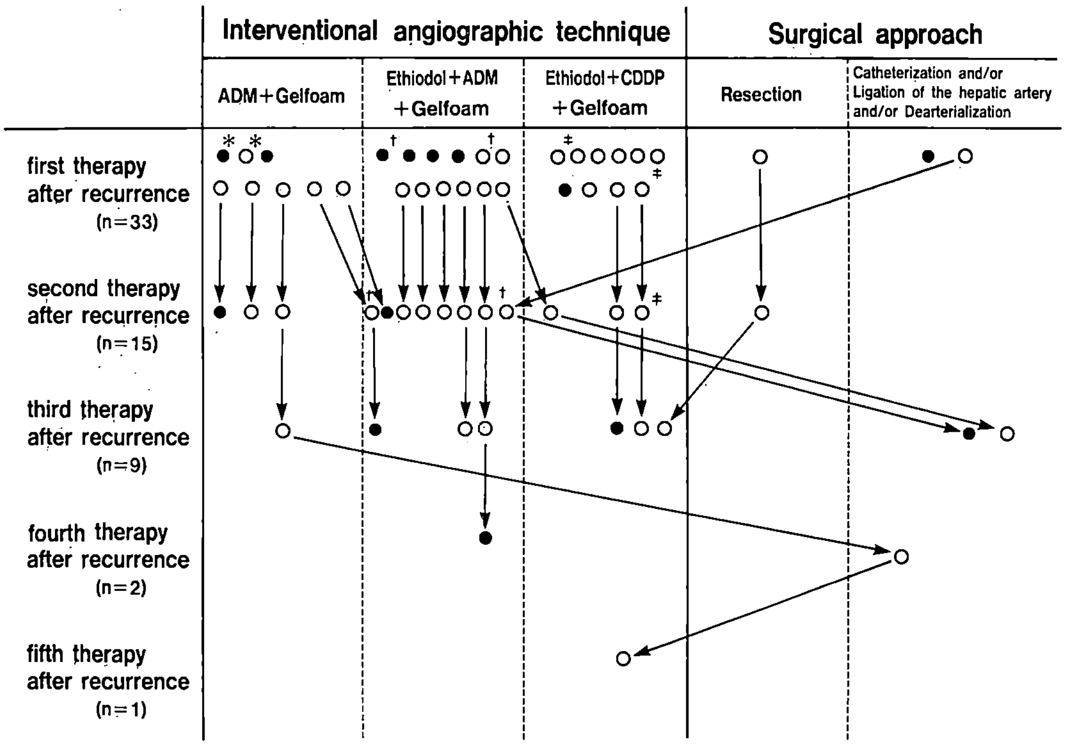

Interventional angiographic technique
Surgical approach
ADM+Gelfoam
Ethiodol+ADM +Gelfoam
Ethiodol+CDDP +Gelfoam
Resection
Catheterization and/or Ligation of the hepatic artery and/or Dearterialization
first therapy after recurrence (n=33)
second therapy after recurrence (n=15)
third therapy after recurrence (n=9)
fourth therapy after recurrence (n=2)
fifth therapy after recurrence (n=1)
*
†
‡

FIG. 4. Regional therapies against intrahepatic recurrence. Closed circle: patients who died, open circle: survivors. *, †, and ‡: anticancer agent alone or anticancer agent plus Ethiodol only. ADM: adriamycin, CDDP: cisplatin.

FIG. 5. Disease-free interval and postrecurrence interval of the patients who received the regional therapy. Closed bar: patients who died, open bar: survivors. A: adriamycin + Gelfoam, B: Ethiodol + adriamycin + Gelfoam, C: Ethiodol + cisplatin + Gelfoam, D: hepatic resection, E: catheterization and/or ligation of the hepatic artery and/or dearterialization.

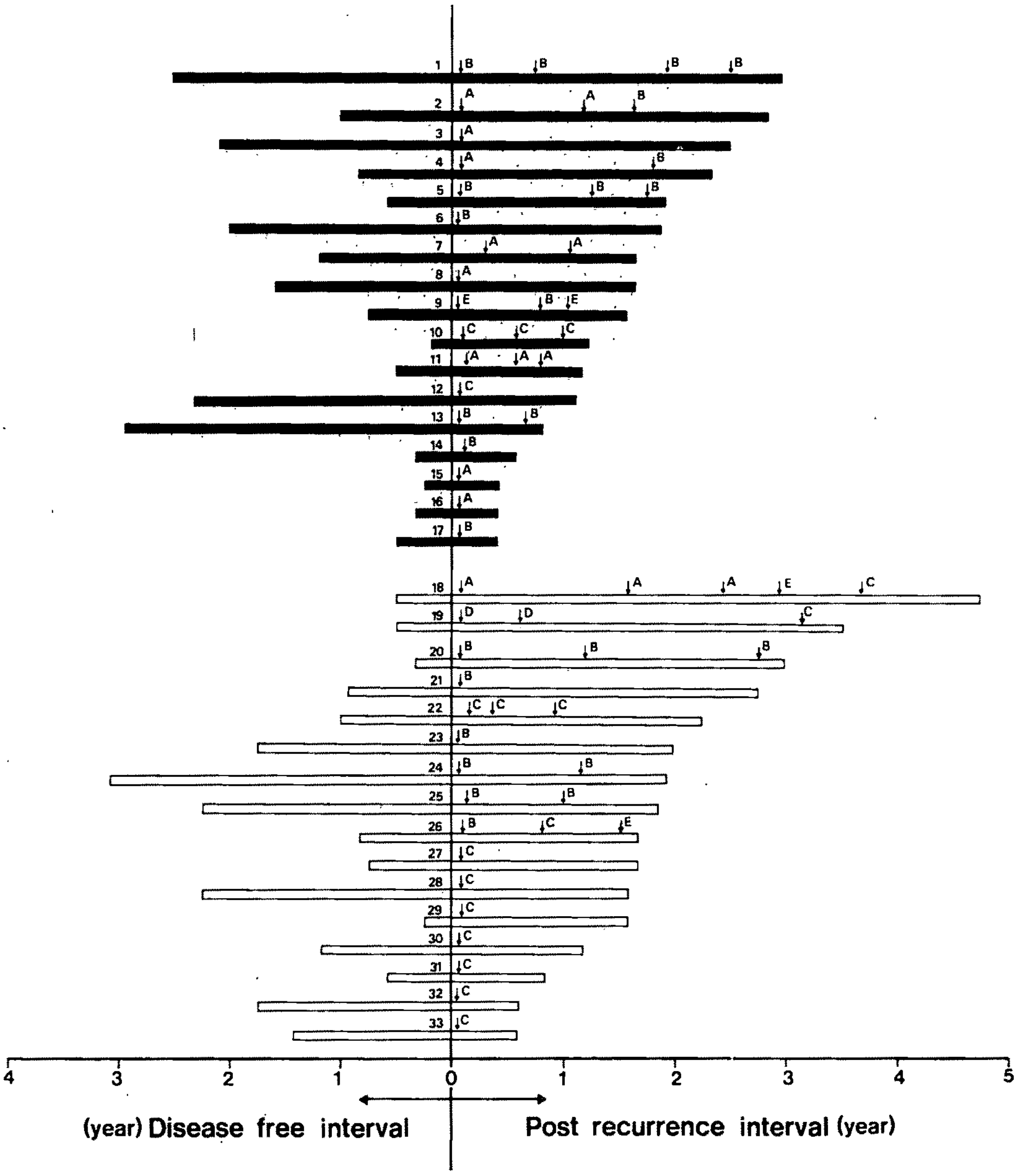
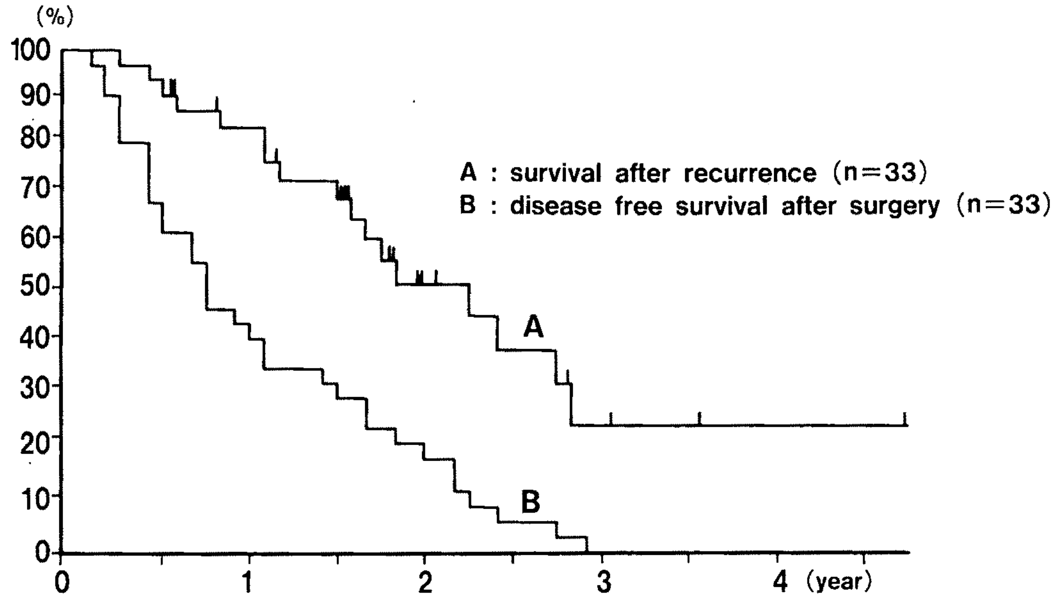


FIG. 6. Survival after recurrence and disease-free survival after surgery of the patients who received the regional therapy. A to B: p < 0.001.



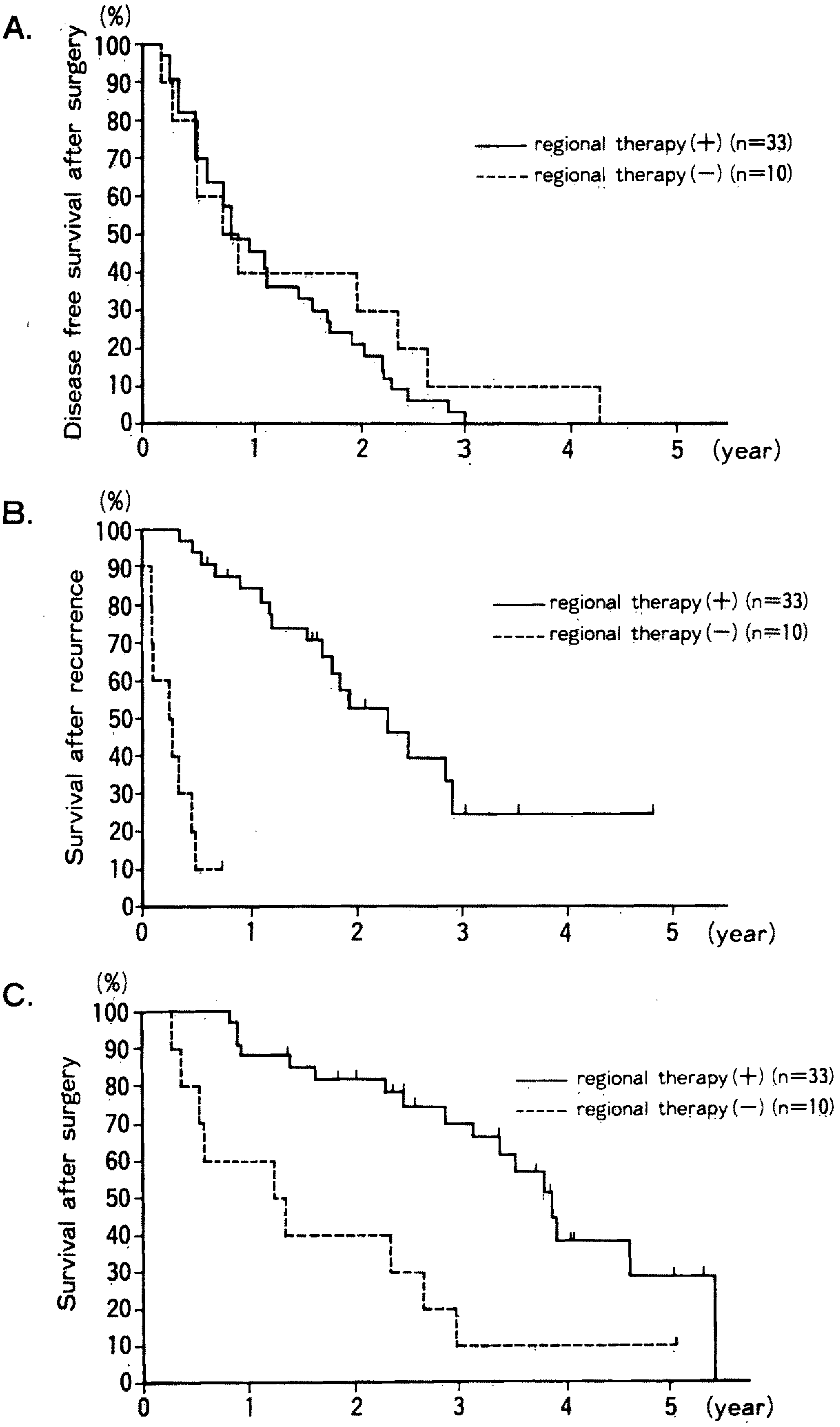


FIG. 7. Comparison of survivals between the patients with and without regional therapies. A: disease free survival after surgery (NS), B: survival after recurrence ($p < 0.001$), C: survival after surgery ($p < 0.01$).

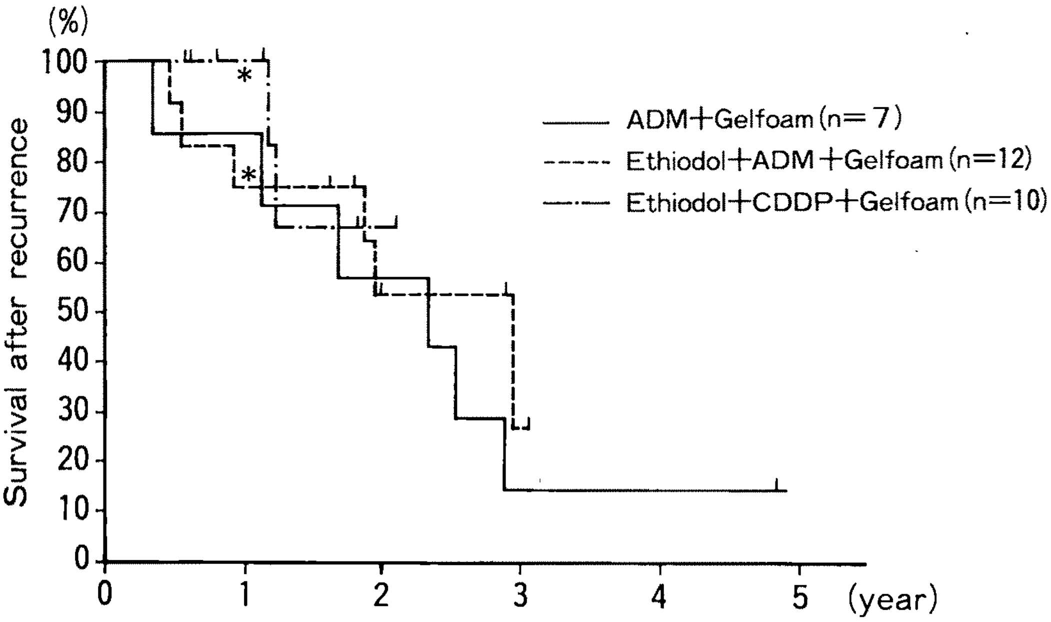


FIG. 8. Comparison of survivals after recurrence among the patients treated by chemoembolization as the first regional therapy after recurrence. *$p < 0.05$.

Comparison between Disease-free Interval and Postrecurrence Interval

Disease-free interval and postrecurrence interval were compared in the 33 patients who received the regional therapy against the intrahepatic recurrence (Fig. 5). In 17 patients who had already died, the median value of the disease-free interval was 13 months and that of the postrecurrence interval was 19 months. Thirteen patients (76%) had longer postrecurrence intervals than disease-free intervals. Moreover, in the 16 patients who are still living, the postrecurrence intervals of the 11 patients (69%) have already been longer than their disease-free intervals. Survival after recurrence and disease-free survival after surgery of these 33 patients were calculated (Fig. 6). The 50% survival rate of the former group of patients was 27 months and that of the latter group was 9 months. The difference between these figures was statistically significant ($p < 0.001$).

Comparison of Survivals between the Patients with and without Regional Therapies

Disease-free survival after surgery, survival after recurrence, and survival after surgery were compared between 33 patients who received the regional therapies and 10 patients who did not (Fig. 7A–C). There was no statistically significant difference between the two groups regarding the disease-free survival (Fig. 7A). The 50% survival after recurrence in the patients receiving regional therapies was 27 months, and the 1-, 2-, 3-, and 4-year postrecurrence survival rates were 84%, 53%, 25%, and 25%, respectively. On the other hand, survival of the patients without the regional therapies was 3 months, and the longest survival was 9 months after recurrence. The difference between these figures was statistically significant ($p < 0.001$) (Fig. 7B). The 50% survival after surgery of the treated patients was 47 months, and the 1-, 3-, and 5-year survival rates were 87%, 70%, and 30%, respectively, whereas that of the untreated patients was 15 months with the 1-, 3-, and 5-year rates of 60%, 10%, and 10%, respectively. The difference between these two figures was also statistically significant ($p < 0.01$) (Fig. 7C).

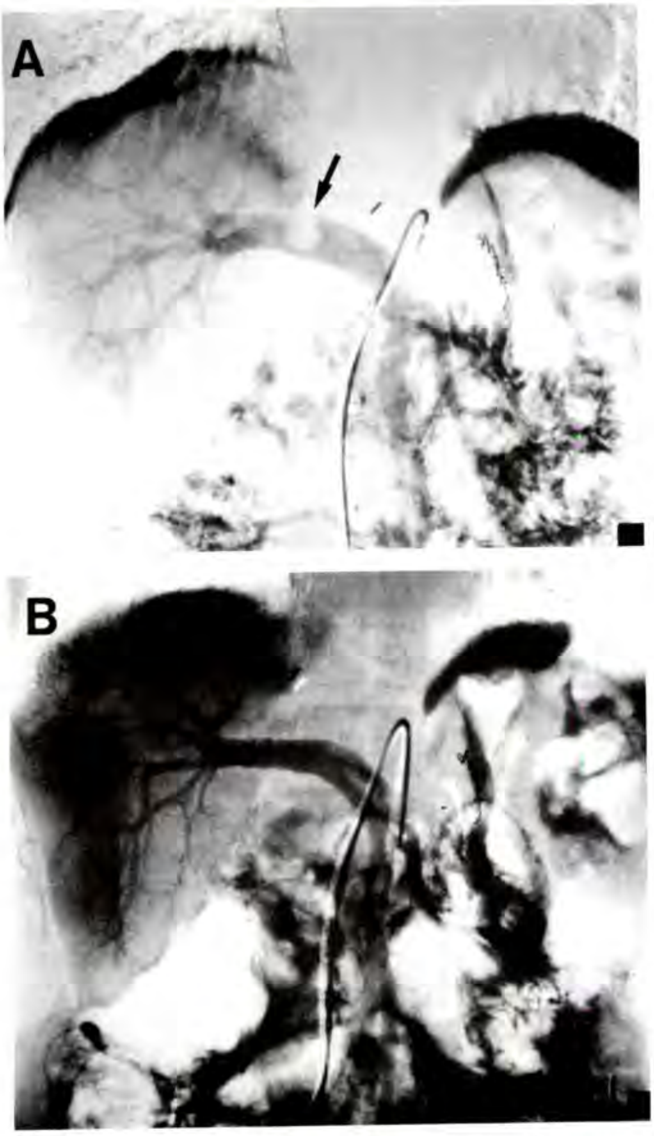
Comparison of Postrecurrence Survivals among the Patients Treated by Three Chemoembolization Regimens

Survivals after recurrence were compared among the three groups treated by interventional angiographic technique as the first regional therapy after recurrence (Fig. 8). There were no statistically significant differences among these figures, but the 1-year survival rate of the group treated by Ethiodol, CDDP, and Gelfoam was significantly better than that of the group treated by Ethiodol, ADM, and Gelfoam ($p < 0.05$).

Case Reports

Case 1

This 59-year-old male patient had partial hepatic resection of anterior and medial segment under the diagnosis of HCC in June 1981. The main tumor was 6.0 × 5.0 cm and was surrounded with many daughter nodules in the resected specimen. In January 1982, recurrent lesions were found in the liver remnant through US and hepatic angiography. The patient received chemoembolization with Gelfoam containing 50 mg of ADM after the angiography. Afterwards, the same therapy was repeated twice for the relapse. In July 1984, the celiac angiogram showed the complete obstruction of the common hepatic artery, but the superior mesenteric arteriogram showed collaterals from the pancreaticoduodenal arcades (PDA) and gastroduodenal artery (GDA) to the proper hepatic artery. He had an infusion of 50 mg of ADM alone from the catheter placed in the inferior pancreaticoduodenal artery due to the failure of superselective catheterization. In



FIGS. 9A and B. Hepatic portogram of Case 2. *A.* Hepatic portogram before the third operation. Arrow points to the defect of the portal trunk by tumor embolus. *B.* Hepatic portogram after the third operation. No tumor embolus is observed.

October 1984, the cannulation into the proper hepatic artery was performed surgically. Three times the patient received an intra-arterial infusion of ADM concomitantly with angiotensin II.[15] However, because the extravasation of the drug by the penetration of the tip of the catheter occurred, the treatment had to be discontinued. In September 1985, the superior mesenteric angiogram showed the collaterals from PDA, GDA, and epicholedochal arterial plexuses into the liver. At this time, as the tip of the catheter was advanced to GDA through PDA, the chemoembolization using Ethiodol, CDDP, and Gelfoam was done. Regardless of the development of intrahepatic recurrences 7 months after hepatic resection, the patient is still alive more than 5 years after surgery.

Case 2

This 69-year-old male patient, who had HCC with liver cirrhosis, had partial resection of anterior segment in September 1982. In June 1983, as a single tumor was found in the lateral segment of the liver, he had lateral segmentectomy. Moreover, in March 1984, the existence of a tumor embolus in the trunk and the left branch of the portal vein was detected through US. Hepatic portogram demonstrated a round defect of contrast medium in the portal trunk and the disappearance of the left portal vein (Fig. 9A). The medial segmentectomy and embolectomy in the portal trunk were performed in April 1984. Hepatic portogram taken after surgery exhibits removal of the tumor embolus in the portal trunk (Fig. 9B). In May 1986, a small focus was discovered in the posterior segment, and he received the chemoembolization using Ethiodol, CDDP, and Gelfoam. The patient is still alive more than 4 years after his first surgery.

Discussion

Lee et al.[12] reported that the tumor size did not affect the patients' survival but an adequate margin of the tumor specimen prolonged the survival significantly longer than that of inadequate margins. However, even the 4-year survival rate of the adequate margin group was under 40%. In our study, the size of the tumor, when over 2 cm in diameter, and the extent of hepatic resection did not affect the incidence of the patients' recurrence (Fig. 2 and Fig. 3). These findings indicate that it is nearly impossible to control the cancerous lesion of the patients with cirrhosis completely by hepatic resection alone. As an explanation, it is conceivable that the microscopic intrahepatic metastasis has already occurred in an earlier stage or the cirrhotic liver has multicentric metachronous or unnoticed synchronous carcinogenesis. Whether or not, at the current stage, slightly wider and more extensive resection within the limitation of the reserve capacity of the cirrhotic liver does not seem to avoid the occurrence of intrahepatic recurrence in any significant frequency.

Therefore, to obtain a successful long-term survival after surgery for cirrhotic patients with HCC, it is necessary to detect earlier intrahepatic recurrences using close follow-ups and to repeat active regional therapies against the recurrent lesions. Lee et al.[12] reported that the survival of the patients who had more than two operations was significantly longer than that of the patients who had only a single operation. Nagasue et al.[16] reported recently that a second hepatic resection is a possible and meaningful method for patients with recurrent HCC in the liver remnant. Their findings also suggest effectiveness of the regional therapy for recurrent liver. In the current study, only one patient had resection three times (Case 2). Practically speaking, the number of patients for whom the second hepatic resection in the treatment of recurrent HCC is possible are few because of the multiple recurrent foci, progressive liver dysfunction, and the patients' rejection. We mainly chose the transcatheter arterial chemoembolization as the first-choice therapy for most of the patients with recurrence. Recently, arterial embolization and chemoembolization have been considered to be useful therapeutic procedures for HCC. Yamada et al.[17] reported the treatment of 120 patients with unresectable HCC by arterial embolization with Gelfoam. The 1-, 2-, and 3-year cumulative survival rates were 44%, 29%, and 15%, respectively. More recently, many articles from Japan have recommended chemoembolization using ethiodized oil, a chemotherapeutic agent, and Gelfoam.[18,19] Results using these methods were superior to embolization with Gelfoam alone. A method using ethiodized oil, CDDP, and Gelfoam was developed by us as one of the regimens of chemoembolization, and its efficacy has been reported previously.[14] These angiographic techniques can be performed more safely and easily than surgical resection for patients with cirrhosis.

By repeating the regional therapies against the intrahepatic recurrences, many of our patients had longer postrecurrence intervals than disease-free intervals. Consequently, the 5-year cumulative survival rate of all patients who had the radical operation was 40%. This survival rate is better than any other reported by surgeons in Asian countries. Our results obtained by regional therapies for the recurrent liver may raise a question as to whether surgery is the first-choice therapy for the cirrhotic patients with HCC. Surgery is generally considered to be superior to any other therapeutic procedures, and we have observed some cirrhotic patients with HCC who have survived over 5 years without recurrence through surgical procedures alone. To settle this problem, a control study will be necessary between surgery alone and chemoembolization alone in patients at resectable stages. As long as adequate survival data of patients treated by chemoembolization do not confirm efficacy to establish it as an alternative to surgery, we believe hepatic resection should be chosen as a first-choice therapy.

We also believe that prevention of cancer recurrence is more important and realistic than treatment after recurrence. However, genuine value of postoperative adjuvant chemotherapy has not yet been enlightened. Since the reserve capacity and the regeneration ability of the cirrhotic liver are remarkably poor, the use of cytotoxic drugs immediately after hepatic resection may delay the regeneration of residual liver and advance the liver dysfunction.[20,21] Therefore, currently we consider that repeating active regional treatments against intrahepatic recurrences after hepatic resection constitutes the best means for the management of HCC coexisting cirrhosis to gain a long-term survival after surgery.

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Emergency Portacaval Shunt for Variceal Hemorrhage

A Prospective Study

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Emergency portacaval shunt for variceal bleeding is associated with a high operative mortality, particularly if used as a last resort. Because of this, a strong case has been made against emergency shunt. This report describes an experience with emergency portacaval shunt for the treatment of variceal bleeding when used systematically after hemodynamic stabilization and control of the bleeding episode with balloon tamponade, if necessary, in patients with mild or moderate liver disease. The population studied comprised 62 consecutive patients who rebled from varices while participating in a controlled trial of propranolol for the prevention of rebleeding. Of the 62 patients, nine died of massive hemorrhage and 53 survived the hemorrhage. Of the 53 survivors, 11 had severe liver disease and were not considered for shunt surgery. Of the remaining 42 patients with mild or moderate liver disease, 36 had emergency central portacaval shunt. The interval between endoscopic diagnosis of variceal bleeding and surgery averaged 19 ± 3 hours (mean ± SE). The operative mortality rate, defined as in-hospital mortality, was 19%. One- and 2-year survival rates were 78% and 71%, respectively. The incidence of postoperative hepatic encephalopathy was 36%; all patients responded favorably to protein restriction and lactulose. Thus, under specific conditions, emergency portacaval shunt results in an acceptable long-term survival rate. In patients with mild or moderate liver disease, emergency portacaval shunt should be considered when other forms of treatment for the prevention of variceal rebleeding have failed.

From the Liver Unit and Departments of Medicine, Surgery, and Epidemiology, Hôpital Saint-Luc and Université de Montréal, Montreal, Canada

HEMORRHAGE FROM ESOPHAGEAL VARICES is a life-threatening complication of portal hypertension in patients with cirrhosis. Among patients admitted for variceal hemorrhage, 80% will rebleed and 60% will die within 1 year.[1] In addition, the risk of rebleeding and death is much higher within the days and weeks after the initial hemorrhage, and decreases thereafter.[1,2] Thus, any substantial improvement in survival must rely on maneuvers that can be used early after the initial bleeding to prevent recurrences.

Four randomized trials of therapeutic portacaval shunt have shown no significant improvement in survival with shunting,[3] but in all four studies, randomization took place at some time, days to weeks, after presentation for bleeding, *i.e.*, beyond the period of the highest mortality. Emergency portacaval shunt has been advocated by Orloff and Bell[4] to treat cirrhotic patients with acute variceal bleed. The high operative mortality rate (40–50%) is a major deterrent to this procedure, particularly if used as a last resort.[5,6] However, patients with untreated active bleeding have comparable mortality rates,[7] and there are no controlled trials comparing emergency shunt with conservative medical therapy. Despite this lack of adequate data, a strong case has been made against emergency portacaval shunt.

Besides early recurrence, the severity of liver failure is the other major determinant of mortality rate in cirrhotic patients with variceal hemorrhage.[8] The prognosis in patients with severe liver disease is usually dismal and it seems unlikely that any therapeutic strategy can significantly improve their survival.

In this report, we describe our experience with emergency portacaval shunt in patients with variceal hemorrhage and mild to moderate liver disease. All patients were part of a negative clinical trial of propranolol, and

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data were collected prospectively at the time of variceal rebleeding. Our results suggest that under well-defined conditions, emergency portacaval shunt is a valid therapeutic alternative.

Materials and Methods

During a 3-year period, 79 adult patients admitted to Saint-Luc Hospital for variceal hemorrhage were entered into a controlled trial of propranolol for the prevention of variceal rebleeding. During an average follow-up of 692 ± 78 days (mean ± SE), 62 of 79 patients rebled. The average interval between the first bleeding episode and rebleed was 91 ± 20 days. There was no difference in the rebleeding rate between patients treated with propranolol and patients treated with placebo. Detailed results of this trial have been published elsewhere.[9] The endpoint of the trial was rebleeding from varices. In patients who rebled, drug treatment was discontinued and alternative treatments were used. We decided *a priori* that, if possible, patients who rebled and who were in good condition would have an emergency central portacaval shunt, whereas patients with severe liver disease would be treated by endoscopic sclerotherapy with intravariceal ethanolamine. However, available alternatives were explained to the patient, who made the final decision. The 62 patients who rebled form the basis of this report.

The severity of liver disease at the time of rebleeding was assessed by the Child-Turcotte classification (CTC) as modified by Di Magno et al.[10] In this modification, each of five variables (ascites, encephalopathy, serum albumin, serum bilirubin, and prothrombin time) is given a value of 1, 2, or 3 for increasing abnormality, and the values summed over the five variables for each patient. Thus, the best possible score is 5 and the worst is 15. Mild liver disease (class A) is defined as a score of 5–7, moderate liver disease (class B) as a score of 8–10, and severe liver disease (class C) as a score of 11 or greater. Bleeding was treated initially with blood transfusions as required, and balloon tamponade if necessary until definitive treatment by surgery or sclerotherapy. Surgery was performed by one of four surgeons (LD, RL, ST, and PL) experienced with portacaval shunt surgery.

The diagnosis of hepatic encephalopathy occurring during follow-up was based on clinical criteria according to Trey et al.[11] Encephalopathy was categorized as "spontaneous" (not associated with specific comagenic events) or "induced" (precipitated by gastrointestinal bleeding, drug administration, infection, *etc.*). "Spontaneous" encephalopathy was further categorized as "mild" (easily managed by diet and lactulose or neomycin, not interfering with normal life function) or "severe" (precluding normal activities of daily living).[12]

Survival curves were constructed by the Kaplan-Meier method.[13] Multivariate analysis, using the Cox proportional hazard model[14] with a stepwise procedure was performed to identify variables that had an effect on survival.

Results

The outcome of the 62 patients who rebled from varices is shown in Figure 1. Nine patients died of massive hemorrhage at the time of rebleeding: two patients died at home and seven patients died in the hospital. Of the 53 patients who survived the hemorrhage, 42 had mild or moderate liver disease (CTC class A or B) and 11 had severe (class C) liver disease (Fig. 1).

Severe Liver Disease Group

Eight of the patients with severe liver disease were treated by repeated endoscopic sclerotherapy. All died within 4 months except one patient who had an hepatic transplantation. Three patients were treated by emergency portacaval shunt surgery: two patients chose surgery rather than sclerotherapy, and one patient had shunt surgery because of repeated bleeding after sclerotherapy. All three patients died within 30 days of surgery (2 of liver failure and 1 of sepsis).

Mild or Moderate Liver Disease Group

Of 42 patients with mild or moderate liver disease at the time of rebleeding, 36 had emergency shunt surgery. Two patients had devascularization surgery instead of a shunt because of portal vein thrombosis (1 patient died of postoperative complications and the other was alive at 1 year). The remaining four patients were treated by endoscopic sclerotherapy: one patient refused surgery, one patient had portal vein thrombosis, one patient was 96 years old and had cardiac failure, and a portacaval shunt turned out to be technically impossible at laparotomy in the fourth patient. Two of these four patients were alive at 1 year.

Of the 36 patients who had emergency surgery, 35 had a terminolateral portacaval shunt and one a central splenorenal shunt. Balloon tamponade was used in a majority of patients to control the bleeding episode and obtain hemodynamic stabilization before surgery (Table 1). The interval between the endoscopic diagnosis of variceal bleeding and surgery averaged 19 ± 3 hours (mean ± SE). In five patients, surgery was delayed for more than 48 hours because of infection (N = 4) or delayed patient's consent (N = 1). The operative mortal-

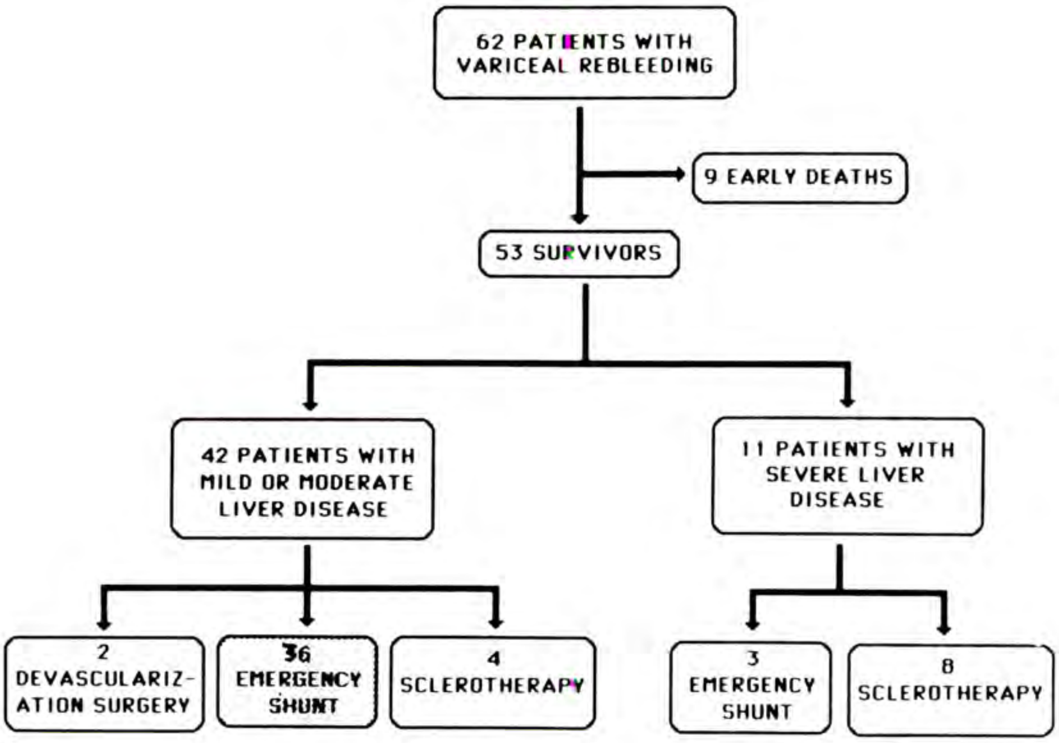
62 PATIENTS WITH VARICEAL REBLEEDING
9 EARLY DEATHS
53 SURVIVORS
42 PATIENTS WITH MILD OR MODERATE LIVER DISEASE
11 PATIENTS WITH SEVERE LIVER DISEASE
2 DEVASCULARIZATION SURGERY
36 EMERGENCY SHUNT
4 SCLEROTHERAPY
3 EMERGENCY SHUNT
8 SCLEROTHERAPY

FIG. 1. Outcome in 62 patients who rebled from varices.

ity rate, defined as in-hospital mortality after surgery, was 19%: three patients died of sepsis, two patients died of liver failure, one patient died of adult respiratory distress syndrome, and one patient died of bleeding after shunt thrombosis. Hepatic encephalopathy occurred in 36% of patients (isolated "induced" episodes in 12% and "spontaneous" in 24%). Encephalopathy responded favorably to protein restriction and lactulose administration in all instances. One- and 2-year survival rates were 78% and 71%, respectively (Fig. 2).

TABLE 1. *Emergency Shunt Surgery in 36 Patients with Mild or Moderate Liver Disease*

Age (years, mean ± SE)	55 ± 2
Etiology of portal hypertension (no. of patients/%)	
Alcoholic cirrhosis	25 (69%)
Nonalcoholic cirrhosis	10 (28%)
Idiopathic portal hypertension	1 (3%)
Severity of liver disease (no. of patients/%)*	
Class A	13 (36%)
Class B	23 (64%)
No. of transfusions for bleeding episode (mean ± SE)	3.5 ± 0.6
No. of patients requiring balloon tamponade for initial control of bleed (no. of patients/%)	20 (56%)
Interval between bleeding episode and surgery (no. of patients/%)	
0–24 hours	23 (64%)
24–48 hours	8 (22%)
>48 hours	5 (14%)
Operative mortality (no. of patients/%)	7 (19%)

* According to DiMagno's modification of the Child-Turcotte classification, see text for details.

Prognostic Factors for Survival

Of the 53 patients who survived the rebleeding episode, 1- and 2-year survival rates were 60% and 56%, respectively. Prognostic variables for the duration of survival were examined by the Cox proportional hazard model. Potential variables examined included age, the severity of liver disease (CTC score), the presence of associated diseases (comorbidity), the presence of active alcoholism, the severity of the bleeding episode (number of transfusions required), and serum creatinine level. The severity of liver disease and serum creatinine level were the only variables found to be of prognostic significance ($p < 0.05$).

Discussion

Our data suggest that portacaval shunt is a valid alternative for the treatment of acute variceal hemorrhage, and that it can be applied in a majority of patients with mild or moderate liver disease, with good long-term results.

In this prospective study, we had planned to use emergency shunt in patients with mild to moderate liver disease. Emergency shunt was not used as a desperate measure in patients who continued to bleed despite conventional treatment, but rather systematically after hemodynamic stabilization and control of the bleed with balloon tamponade. Under these conditions, the operative mortality rate was 19%. The 1-year survival rate of 78% appears comparable to that of similar patients treated by sclerotherapy.[15,16]

Portacaval shunt was highly effective in preventing further variceal hemorrhage, as only one of 36 patients rebled from varices due to thrombosis of the shunt, but the drawback was a 36% incidence of postoperative hepatic encephalopathy. In all instances, encephalopathy responded favorably to protein restriction and lactulose, but was responsible for 13 hospital admissions over a 2-year period. Endoscopic sclerotherapy is not associated with such a high incidence of encephalopathy, but patients often need to be admitted for repeated bleeding until varices are eradicated.[15,17] The extent to which encephalopathy or repeated bleeding alter the quality of life of patients has not been examined.

Our results in patients with severe liver disease were catastrophic no matter which treatment was used. The only long-term survivor was a 28-year-old patient who had an hepatic transplantation 1 month after the bleeding episode. This observation re-emphasizes that the severity of the underlying liver disease is the key determinant to prognosis in variceal hemorrhage. The ominous nature of variceal hemorrhage is also illustrated by the number of patients who died of massive hemorrhage before any therapeutic intervention could be applied (15% in this study). These patients were identified because they were part of a prospective study on rebleeding. Some of them died at home, or in the hospital before any resuscitation measures could be initiated. In other settings, such patients would not be diagnosed and included in a descriptive study of variceal hemorrhage, leading to an underestimation of mortality due to variceal bleeding.

Cello et al.[18] compared emergency shunt with endoscopic sclerotherapy in patients with severe liver disease and found no difference in short-term (1-year) survival between the two groups. A preliminary report by the same investigators also suggests that there is no difference in total health care costs between the groups.[19] In their study, patients were designated as having severe (class C) disease according to the single worst criterion for class C of the five variables measured. In our study, 25 of the 42 patients that we classified as having mild or moderate disease would have been classified as having severe liver disease according to their definition. It is therefore difficult to compare different studies because of such methodological variations.

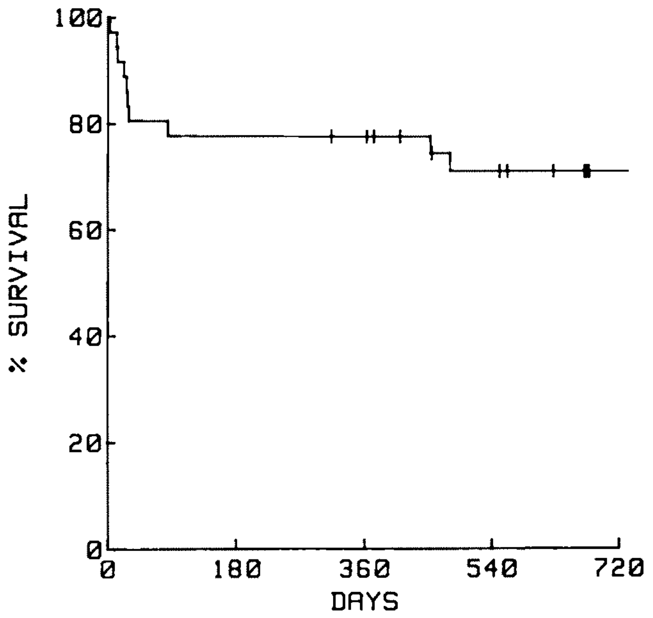

FIG. 2. Cumulative survival after emergency portacaval shunt surgery in 36 patients with mild or moderate liver disease. The short vertical bars represent trial times for patients still alive when last seen.

In summary, our data indicate that in patients with mild or moderate liver disease, emergency portacaval shunt results in an acceptable long-term survival rate. We suggest that emergency shunt surgery should be considered in such patients when other forms of treatment for the prevention of rebleeding have failed. A preliminary report by Warren et al.[20] also suggests that sclerotherapy followed by shunt surgery for sclerotherapy failure results in a significantly improved long-term survival.

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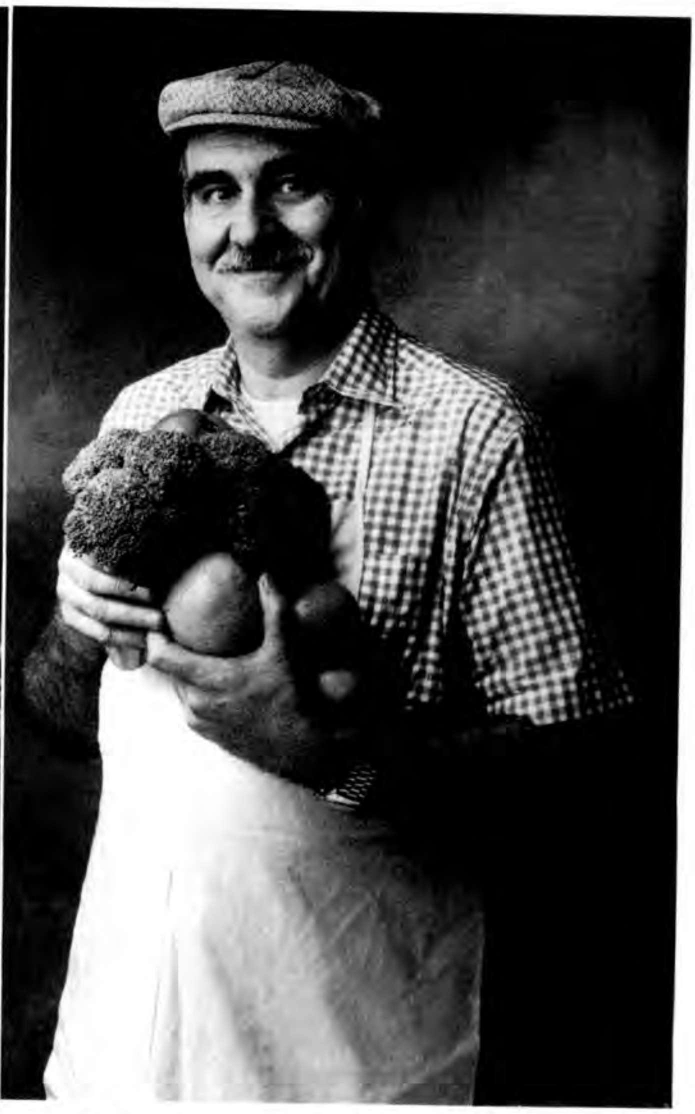

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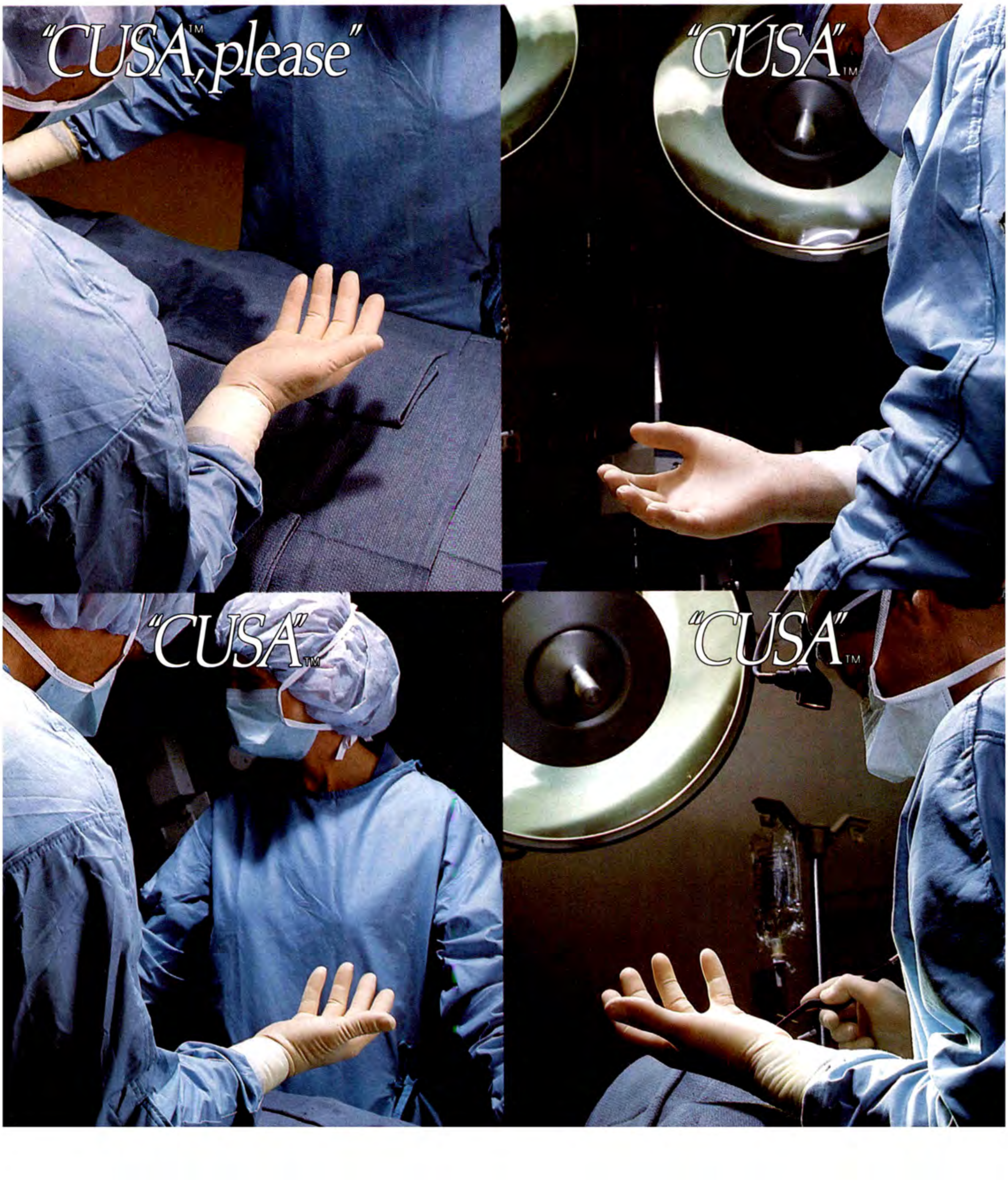

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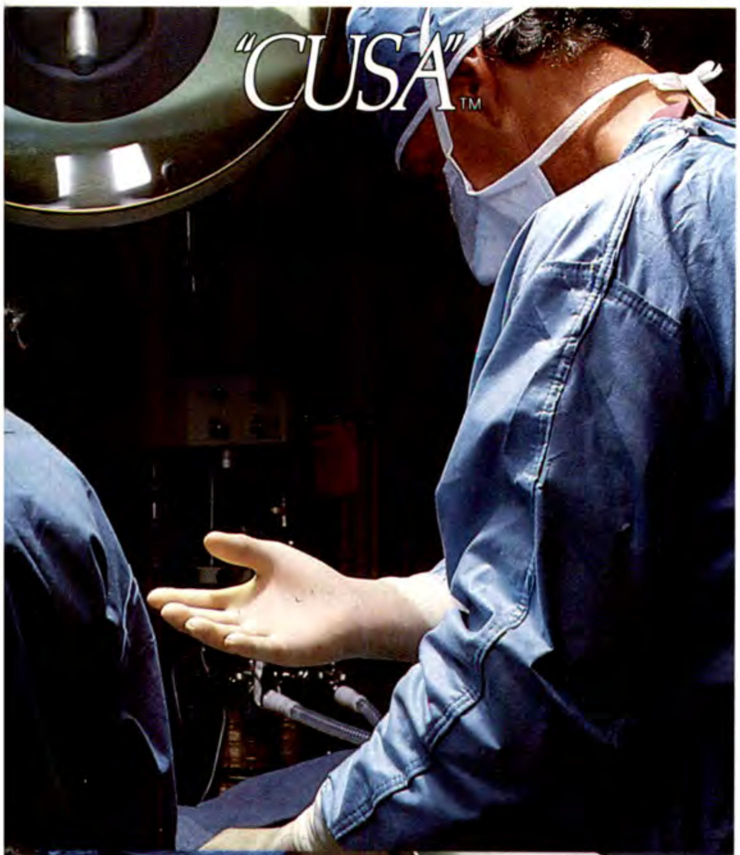

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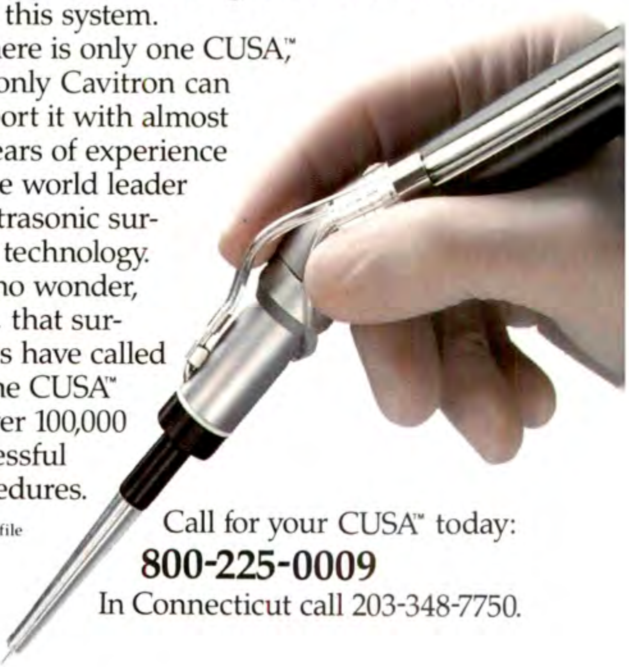

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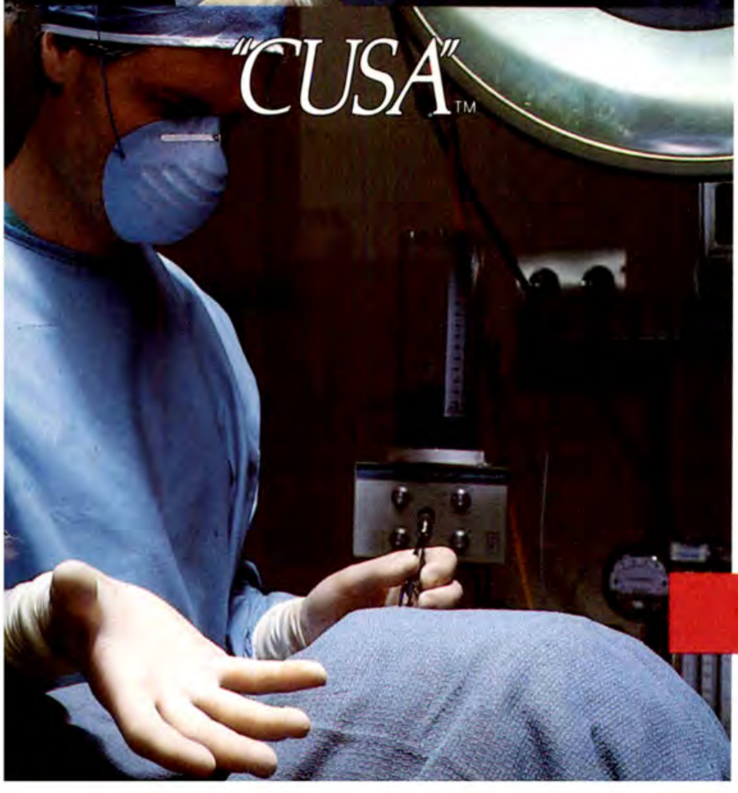

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Comparison of Intraoperative Ultrasonography and Cholangiography in Detection of Small Common Bile Duct Stones

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High-resolution intraoperative ultrasonography was compared with conventional radiographic imaging in the detection of small common bile duct (CBD) stones (<5 mm in diameter). Sixteen mongrel dogs had laparotomy and ligation of distal CBD; 1 week to 10 days later, 0–3 gallstones of varying sizes (2–5 mm) were introduced into the dilated CBD (6–16 mm). High-resolution intraoperative ultrasonography of the CBD and a conventional intraoperative cholangiogram were performed to detect the presence and number of stones. The results of these two tests were evaluated independently by two ultrasonographers and two surgeons. There were 21 true-positive and five false-negative readings by sonogram compared with 17 and 9, respectively, by cholangiogram. Sensitivity of the sonogram was 81% and 65.4% by cholangiogram. Score of accuracy was 1.06 and 1.62 by cholangiogram and 0.81 and 0.87 by ultrasound ($p < 0.05$). Intraoperative ultrasonography was found to be more sensitive in detecting small CBD stones when compared with intraoperative cholangiogram.

COMMON BILE DUCT (CBD) explorations are performed in 10–15% of all routine cholecystectomies.[1] The incidence of unsuspected CBD stones varies from 4–10% even in the absence of traditional clinical indications for CBD explorations.[2-4] The routine use of intraoperative cholangiography has allowed a 50% reduction in the number of CBD explorations with a concomitant two- to three-fold increase in a positive yield.[5-9] Yet despite a routine completion T-tube cholangiogram after a CBD exploration, the incidence of retained common duct stone remains about 4–7%.[10,11] In an attempt to reduce further the incidence of this complication, intraoperative ultrasonography has been suggested as a more accurate method of detecting CBD stones at the time of surgery.[11-19] However, its accuracy when dealing with small stones has been questioned.[18] The aim of this study was to compare high resolution ultrasonography with conventional radiographic imaging in the detection of small CBD stones (<5 mm) in ducts of varying sizes.

From the Long Island Jewish Medical Center, New Hyde Park, and State University of New York at Stony Brook, Stony Brook, New York

Materials and Methods

Human gallstones were obtained from patients at elective cholecystectomy. Twenty-two stones were measured in the greatest diameter. Four stones were 2 mm, seven stones were 3 mm, six stones were 4 mm, and five stones were 5 mm in diameter. Sixteen healthy mongrel dogs weighing between 10 and 20 kg were housed in a thermoregulated environment (23 C) and received dog chow (Ralston Purina Co., St. Louis, MO) and water *ad libitum*. After an overnight fast, the dogs were anesthetized with an intravenous administration of 30 mg of sodium pentobarbital per kilogram of body weight. Under sterile conditions, a midline laparotomy was performed. The CBD was identified and dissected free. A 2-0 silk ligature was placed around the distal CBD to cause dilation of the biliary tract since the normal canine bile duct is too small to admit a 5-mm gallstone. After a period of recovery of 5–10 days, the dogs had a second laparotomy under sodium pentobarbital anesthesia. At this time the CBD measured 6–16 mm in diameter with a mean of 9.5 mm (Table 1). This is comparable to a human CBD. The silk ligature around the distal common bile duct was removed. Human gallstones measuring 2–5 mm were introduced in varying numbers (0–3) into the CBD through a duodenotomy (Table 1). A high-resolution ultrasonography was performed using a 7.5-MHz small parts transducer with a

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TABLE 1. *Number and Size of the CBD and Gallstones*

CBD (N = 16)		Gallstones (N = 22)	
N	Size	N	Size
2	6	4	2
4	7		
3	8	7	3
2	9		
1	10	6	4
2	11		
1	14	5	5
1	16		

short focal length to detect the presence and number of stones in the CBD. Direct contact scans were performed. The transducer was covered with a sterile glove and the CBD was scanned directly using sterile saline in the field. This was followed by a conventional intraoperative cholangiogram. A 25% Hypaque® solution was injected *via* a catheter placed in the CBD through the duodenotomy. The results of the ultrasonographic and x-ray studies were evaluated blindly and independently by two ultrasonographers and two surgeons. The two methods were compared using the incidence of true-positive, true-negative, false-positive, and false-negative as defined in Table 2. Accuracy of both methods was evaluated by using a scoring technique. When the correct number of stones were identified, a score of zero was given. When the number of stones was greater or lesser than the actual number, the score was given as the absolute difference between the observed number and the actual number (*e.g.*, if the actual number was 1 and the observer read it as 3, then the score given was 2).

TABLE 2. *Definitions*

True (+) (TP)	Stones in the duct and read as stones.
True (−) (TN)	No stone in the duct and read as no stone.
False (+) (FP)	No stones but read as stones.
False (−) (FN)	Stones in the duct and read as no stones.

TP = true-positive; TN = true-negative; FP = false-positive; FN = false-negative.

TABLE 3. *Comparison of Intraoperative Cholangiogram and Ultrasound in Detection of Small CBD Stones*

	No. of Observations	
	Sonography	Cholangiography
True-positive	21	17
True-negative	2	3
False-positive	4	3
False-negative	5	9
Total	32	32

TABLE 4. *Indices of Accuracy*

Predictive Value Of:	Ultrasonography	Cholangiography
A positive test $\left(\frac{TP}{TP + FP}\right)$	84%	85%
Sensitivity $\left(\frac{TP}{TP + FN}\right)$	81%	65.4%
Specificity $\left(\frac{TN}{TN + FP}\right)$	33%	50%
Efficiency $\left(\frac{TP + TN}{\text{All tests}}\right)$	72%	62.5%

TP = true-positive; FP = false-positive; TN = true-negative; FN = false-negative.

Results

The mean time required for the actual intraoperative testing was similar for both techniques. Neither high-resolution ultrasonography nor intraoperative cholangiography detected gallstones in the CBD in 100% of the dogs. Ultrasonography yielded 65.6% true-positive and 15.6% false-negative readings compared with 53.1% true-positive and 28.1% false-negative readings for intraoperative cholangiogram (Table 3). In 53% of the dogs, ultrasonography correctly quantitated the number of stones present regardless of the size of the stones. In contrast, conventional intraoperative cholangiography detected the actual number of stones in only 25%. The predictive value of ultrasonography to detect small stones in the CBD was 84% with a sensitivity of 81% (Table 4). For intraoperative cholangiography, the predictive value of the positive test was 85% but its sensitivity was only 65%. The score of accuracy was 1.06 and 1.62 by cholangiography, which was less accurate than ultrasonography. The score of accuracy by ultrasonography was 0.81 and 0.87 (Table 5).

Discussion

The use of routine cystic duct cholangiography has significantly reduced the incidence of negative CBD explorations.[5-9] Intraoperative ultrasonography of the CBD to detect the presence of CBD stones has been shown to be equally effective.[13,15-17] However, with ei-

TABLE 5. *Score of Accuracy of Identifying the Number of Stones*

Observer	1	2	3	4
Method	IOC	IOC	US	US
Mean	1.06	1.62	0.81	0.87
SD	1.06	0.96	0.75	0.88
p value		0.03		

IOC = intraoperative cholangiogram.
US = ultrasound.

ther of these techniques the small size of the CBD stone has been a limiting factor.[18] The validity of this data is questionable for lack of long-term observation of these patients. In a follow-up study on 152 patients with residual intraductal calculi, Hicken and McAllister[10] showed that the initial clinical course provided little information concerning the presence of overlooked stones. In the same study, within 18 months, 60% of the remaining 132 patients required a second operation. With a 5-year follow-up of these patients, 96% or 143 patients required secondary exploration. There were five operative deaths associated with re-exploration of the bile ducts. With the advent of percutaneous extraction of these retained stones, the mortality and morbidity have been decreased but not eliminated. This is why every attempt should be made at the initial operation to remove all possible stones in the CBD. We have shown in this study that the intraoperative use of ultrasound is more sensitive in detecting small CBD calculi compared with the routine cholangiogram. The other advantage of this technique is that there is no radiation hazard, and the probe can be used for as long as necessary to detect the stones. The time required for both procedures was found to be the same in this study.

Our study presents the advantage of verifying the accuracy of these tests as the exact number of stones introduced in each duct was known. Indeed, with intraoperative cholangiogram, nine CBD stones would have been left behind compared with five that would have been left behind by ultrasound. The four false-positive tests by sonogram and three by cholangiogram were considered to be due to the presence of air bubbles. Air bubbles can occur in the CBD during stone introduction by the technique used in this study and interfered more with the ultrasonographic readings. Since no accidental introduction of air into the biliary tree will occur clinically, a much higher specificity than that found in this experimental model would be expected.

The disadvantage of ultrasound is noted to be the need for trained personnel. In previous studies[15-17] it has been shown that with time and familiarity with the technique, surgeons can learn to interpret the findings, thus eliminating the need for a trained ultrasonographer.

In summary, we have presented the results of a comparison between conventional intraoperative cholangiography and ultrasonography in detection of small (<5 mm in diameter) CBD stones. We found intraoperative ultrasound to be more sensitive in detecting small CBD stones compared with intraoperative cholangiography.

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Protein and Energy Metabolism with Biosynthetic Human Growth Hormone after Gastrointestinal Surgery

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The effect of biosynthetic human growth hormone (BSHGH) on postoperative protein and energy metabolism has been studied in patients who had major gastrointestinal surgery. Seven patients received placebo and seven patients received BSHGH, 0.1 mg/kg/24 h, for the first six postoperative days. Mean total nitrogen excretion was significantly lower with BSHGH (31.5 ± 2.4 g N) (2287 ± 160 mmol) than with placebo (42.7 ± 3.1 g N) (3049 ± 219 mmol) over the 6-day study period. The mean daily measured energy expenditure over days 3–6 was higher with BSHGH (31.3 ± 1.8 kcal/kg LBM/24 h) (131 ± 7 kJ/kg LBM/24 h) than with placebo (27.6 ± 0.8 kcal/kg LBM/24 h) (114 ± 2 kJ/kg LBM/24 h). Fat oxidation with BSHGH (2.05 ± 0.26 mg/kg LBM/24 h) was greater than with placebo (1.5 ± 0.17 mg/kg LBM/24 h) and protein oxidation was less with BSHGH (0.68 ± 0.07 g/kg LBM/24 h) than with placebo (0.9 ± 0.09 g/kg LBM/24 h) on days 1–6. Postoperative nitrogen turnover (BSHGH 943 ± 174 mg N/kg LBM/24 h, placebo 557 ± 50 mg N/kg LBM/24 h) (BSHGH 67 ± 13 mmol/kg LBM/24 h, placebo 40 ± 4 mmol/kg LBM/24 h), protein synthesis (BSHGH 5.31 ± 1.09 g prot/kg LBM/24 h, placebo 2.54 ± 0.33 g prot/kg LBM/24 h) and protein breakdown (BSHGH 5.90 ± 1.09 g prot/kg LBM/24 h, placebo 3.48 ± 0.31 g prot/kg LBM/24 h) were greater with BSHGH. On the first postoperative day serum insulin and blood glucose levels were higher with BSHGH than with placebo, and on days 4 and 7 serum somatomedin-C levels were significantly elevated. This study shows that BSHGH alters postoperative protein and energy metabolism by reducing protein oxidation and increasing fat oxidation with raised rates of whole body nitrogen turnover.

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CUTHBERTSON'S DESCRIPTION of increased excretion of nitrogen, sulphur, phosphorus, and calcium after injury, which implied breakdown and oxidation of protein greater than could be accounted for by damage at the injury site alone, has led to the concept that a systemic response to injury exists.[1] This results in increased protein and energy substrate oxidation and an increased metabolic rate.[2] Neuronal and hormonal factors have been implicated in the mediation of this response.[3] The net effect of these changes is to erode protein and energy substrate stores at a time when nutritional intake is often reduced. If these resources are already reduced at a time of injury, the ability to heal wounds, combat infection, and breathe adequately may be impaired, leading to increased morbidity and mortality.[4] Even the well nourished may experience periods of debility after the injury of major surgery, which may relate to reduction of protein reserves and energy stores.[5]

Shortly after its identification, growth hormone was shown to have anabolic effects on protein metabolism, and Cuthbertson et al. were able to abolish negative nitrogen balance in fed rats subjected to fracture of the femur by using a bovine pituitary extract.[6] Human pituitary growth hormone has been investigated in the context of surgery by Johnson and Hadden[17] and Roe and Kinney[8] and in major burns by Soroff et al.[9] and Wilmore et al.[10] Further study has been limited by the availability of human pituitary hormone. Biosynthetic human growth hormone (BSHGH) (Somatonorm, KabiVitrum, Stockholm, Sweden) produced by recombinant DNA technology from an *Escherichia coli* host, has become available recently. BSHGH is identical to human growth hormone but with the addition of a methionyl residue at the N-terminal position.

This study investigates the effects of BSHGH on energy substrate and whole body protein metabolism in patients who have major gastrointestinal operations without nutritional support.

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TABLE 1. *Patient Details*

Patient	Sex	Age (yrs)	Weight (kg)	LBM (kg)	Diagnosis	Operation
Patients receiving BSHGH						
2	F	29	59	42	Duodenal ulcer	Partial gastrectomy
5	M	72	76	53	Carcinoma rectum	A/P resection
7	M	52	66	48	Duodenal ulcer	Partial gastrectomy
11	M	76	79	57	Chronic jejunocolic fistula	Jejunocolic resection
13	F	75	43	32	Colovaginal fistula	Sigmoid colectomy
15	F	59	64	51	Carcinoma sigmoid colon	Left hemicolectomy and hysterectomy
16	M	73	81	62	Carcinoma sigmoid colon	Left hemicolectomy
Mean ± SD		62 ± 17	67 ± 13	49 ± 10		
Patients receiving placebo						
1	M	66	72	57	Carcinoma rectum	Anterior resection
3	F	71	64	44	Carcinoma stomach	Total gastrectomy
4	M	56	90	66	Prior resection for diverticulitis	Reversal of Hartmann's
9	F	75	53	37	Carcinoma cecum	Right hemicolectomy
10	F	86	63	41	Carcinoma sigmoid colon	Left hemicolectomy
12	F	51	56	45	Rectovaginal fistula	A/P resection
14	M	71	62	52	Carcinoma esophagus	Ivor-Lewis
Mean ± SD		68 ± 12	66 ± 12	49 ± 10		

LBM = lean body mass. A/P = abdominoperineal.

Patients and Methods

Sixteen patients due to have major gastrointestinal surgery were allocated at random to receive 0.1 mg/kg of BSHGH or placebo by intramuscular injection at 8:00 P.M. on the day of operation and at the same time for the following 6 postoperative days. Patients who were diabetic, had disturbed liver function, were taking steroids, had sepsis, weight loss of more than 10%, or disseminated malignancy were not considered for study. Two patients had development of septic complications during the course of the study and were excluded from further analysis. Seven patients received BSHGH and seven patients received placebo. The details of sex, age, weight, and lean body mass (LBM) from skinfolds,[11] diagnosis, and operative procedures are shown in Table 1. All patients had an uncomplicated postoperative course during the study. Postoperative analgesia was provided by continuous intravenous morphine sulphate (six in each group) or by morphine epidural injection.

In the preoperative studies, patients were allowed fluids by mouth, to provide 400 kcal/24 h with negligible nitrogen intake. After operation they received a regimen of saline and 5% dextrose solution providing 400 kcal/24 h (1675 kJ/24 h). Water by mouth was introduced when indicated and dietary intake was begun after the sixth day.

Blood samples were drawn for substrate and hormone levels on the control day before operation and on the first, fourth, seventh, and ninth postoperative days between 8:00 A.M. and 9:00 A.M.

Indirect calorimetry was done before operation and on the first 6 postoperative days between 10:00 A.M. and 12:00 P.M. Resting energy expenditure (REE) was determined from oxygen consumption and carbon dioxide production, using Weir's formula.[12] Oxygen and carbon dioxide concentration were measured with paramagnetic and infrared analysers, respectively, gas flow was measured by a Fleisch pneumatochograph incorporated in a mobile system giving a visual display and a continuous printout of results (Calostar, Fenyves & Gut, Basel, Switzerland[13]). Rates of substrate oxidation were calculated from oxygen consumption, carbon dioxide production, and urinary nitrogen excretion by MacHattie's formulae.[14]

Urine for total nitrogen excretion was collected throughout the study period. Total nitrogen was measured by a semiautomated Kjeldahl technique. Nitrogen turnover was measured before operation and on the third to fourth postoperative days using a primed continuous infusion of ^{15}N glycine for 24 hours.[15] Isotope enrichment of urinary urea over the second 12-hour period of infusion was measured by mass spectrometry. Whole body nitrogen turnover was calculated by dividing the infusion rate of ^{15}N tracer by the urinary urea enrichment with ^{15}N at plateau.[16] Whole body protein synthesis was derived by subtracting total urinary nitrogen excretion from turnover. In the absence of nitrogen

TABLE 2. *Total Urinary Nitrogen Excretion, g N/24 h (mmol/24 h)*

Day	0	1	2	3	4	5	6
Placebo	5.9 ± 1.5 (422 ± 107)	8.6 ± 0.6 (616 ± 43)	8.0 ± 1.4 (572 ± 97)	7.3 ± 1.0 (517 ± 68)	7.0 ± 0.8 (497 ± 57)	6.6 ± 1.7 (469 ± 122)	5.3 ± 0.8 (378 ± 57)
BSHGH	5.4 ± 0.8 (387 ± 58)	7.0 ± 1.0 (501 ± 70)	6.8 ± 1.2 (485 ± 89)	4.4 ± 0.4* (315 ± 25)*	4.5 ± 1.0 (318 ± 74)	5.0 ± 1.0 (354 ± 65)*	3.9 ± 0.6 (277 ± 45)

* $p < 0.05$.

intake, whole body protein breakdown corresponds to the rate of nitrogen turnover. Synthesis and breakdown values are converted to grams of protein by multiplying by 6.25. Serum growth hormone, insulin, and somatomedin-C were each measured by radioimmunoassay. Blood glucose was measured by the glucose oxidase method. Results are expressed as mean and SEM. Statistical analysis is nonparametric by the Mann-Whitney U test.

Informed consent was obtained from the patients and the study was approved by the District Ethical Committee.

Results

No adverse effects attributable to the studies or the giving of placebo or BSHGH were encountered. For technical reasons, nitrogen turnover studies were not completed in the preoperative period on three patients (2 placebo, 1 BSHGH) and one patient (BSHGH) in the postoperative period. Total nitrogen excretion over the first 6 postoperative days was 31.5 ± 2.4 g (2267 ± 160 mmol N) for those receiving BSHGH, significantly less than 42.7 ± 3.1 g (3049 ± 219 mmol N) for those with placebo ($p < 0.01$). Results for each day are shown in Table 2 and Figure 2. The mean REE on days 1 and 2 of 28.8 ± 1.4 and 31.7 ± 1.8 kcal/kg LBM/24 h (121 ± 6 and 133 ± 9 kJ/kg LBM/24 h) with placebo and BSHGH, respectively, were not significantly different, but over days 3–6 the REE of 31.3 ± 1.8 (131 ± 7 kJ/kg LBM/24 h) with BSHGH was significantly higher than that with placebo (27.6 ± 0.8, $p < 0.05$) (114 ± 2 kJ/kg LBM/24 h). Although respiratory quotient over days 1–6 was consistently lower in patients receiving BSHGH (0.79 ± 0.02) than patients receiving placebo (0.81 ± 0.02), the difference was not significant. Fat oxidation (BSHGH 2.05 ± 0.26 g/kg LBM/24 h and placebo 1.51 ± 0.17) was significantly higher with BSHGH (Fig. 1). Carbohydrate oxidation (BSHGH 2.10 ± 0.36 g/kg LBM/24 h and placebo 2.09 ± 0.36) was similar and corresponded to dextrose infusion rates of 2.11 ± 0.21 g/kg LBM/24 h for BSHGH and 2.12 ± 0.17 for placebo; protein oxidation (calculated from nitrogen excretion, Fig. 2) was significantly lower with BSHGH than with placebo (0.68 ± 0.07 g/kg LBM/24 h and placebo 0.92 ± 0.09, mean for days 1–6, $p < 0.05$).

Whole body nitrogen turnover, protein synthesis, and breakdown results are shown in Table 3. All values were similar in the preoperation period but after operation, nitrogen turnover, protein synthesis, and breakdown rates were significantly higher in the group receiving BSHGH. In five patients receiving placebo and six patients receiving BSHGH in whom nitrogen turnover was measured before and after operation, turnover decreased to a mean of 75% (range: 61–87%) of control in those with placebo, whereas with BSHGH turnover in-

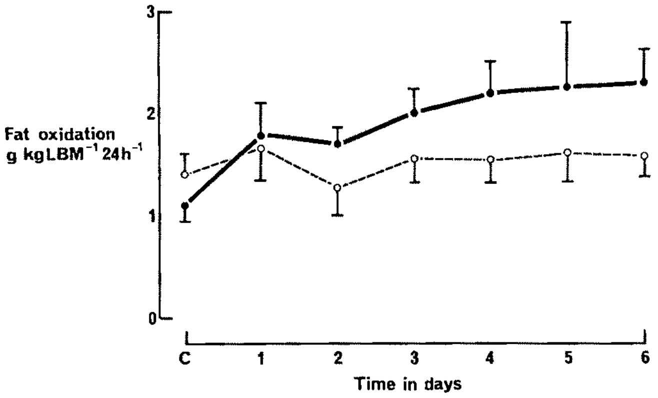

FIG. 1. Fat oxidation with BSHGH (● —— ●) and placebo (O --- O) for the control preoperative day (C) and postoperative days 1–6 expressed as mean ± SEM.

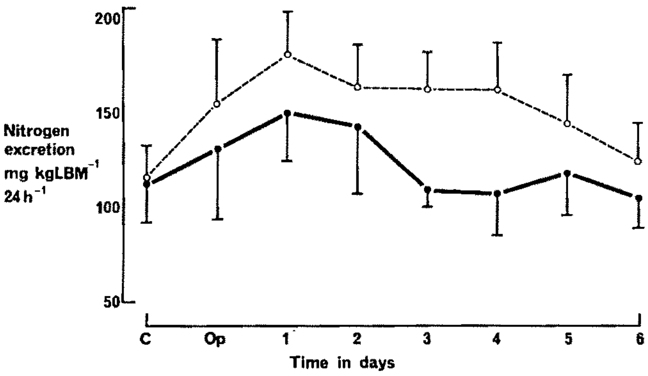

FIG. 2. Total urinary nitrogen excretion with BSHGH (● —— ●) and placebo (O – – – O) for the control preoperative day (C) and postoperative days 1–6 expressed as mean ± SEM.

TABLE 3. *Results of Whole Body Protein Metabolism Measurements (Mean ± SEM)*

	No. of Patients	Nitrogen Turnover mg/kg LBM/24 h (mmol/kg LBM/24 h)	Protein Synthesis g/kg LBM/24 h	Protein Breakdown g/kg LBM/24 h
BSHGH				
Before operation	6	764 ± 66 (55 ± 51)	4.04 ± 0.48	4.78 ± 0.41
After operation	6	943 ± 174* (67 ± 13)	5.31 ± 1.09*	5.90 ± 1.09*
Placebo				
Before operation	5	815 ± 78 (58 ± 6)	4.31 ± 0.54	5.09 ± 0.44
After operation	7	557 ± 50 (40 ± 4)	2.54 ± 0.33	3.48 ± 0.31

* $p < 0.05$ (Postoperative placebo *vs.* postoperative BSHGH).

creased to a mean of 126% (range 81–212%). After operation, whole body protein synthesis expressed as a percentage of breakdown was higher with BSHGH (89 ± 3) than placebo (72 ± 5, $p < 0.05$). The preoperative values were 84 ± 4 and 84 ± 3, respectively.

Serum growth hormone, somatomedin-C, and insulin were all raised in those receiving BSHGH as shown in Table 4. Elevations in serum growth hormone and insulin levels were significant on the first postoperative day and returned to control values by the ninth day, 3 days after the study period. The raised levels of somatomedin-C in patients receiving BSHGH became significant on the fourth and seventh days and were still significantly higher than those of patients receiving placebo on the ninth day. These changes in hormonal profile were accompanied by elevated blood glucose in patients receiving BSHGH (Table 4), which was sufficient to produce slight glycosuria in some patients.

Discussion

The reduction in nitrogen excretion and elevation of metabolic rate and of fat oxidation shown in this study are in keeping with the findings of Cuthbertson et al.[6] and of Roe and Kinney,[8] confirming that BSHGH has similar metabolic effects to growth hormone derived from pituitary glands. In contrast, the study of Johnston and Hadden failed to show an improvement in nitrogen balance with pituitary growth hormone after herniorrhaphy.[7] The lesser degree of trauma, and resulting magnitude of negative nitrogen balance, occurring with hernia repair may explain the difference from the current study. Soroff et al.[9] and Wilmore et al.[10] both demonstrated increased retention of nitrogen, elevation of metabolic rate, and decreased respiratory quotient in severely burned patients given growth hormone.

Initially, Wilmore suggested that adequate nutritional

TABLE 4. *Serum Hormone and Blood Glucose Levels*

Day	0	1	4	7	9
Serum growth hormone,* μ/L					
BSHGH	3 (3–36)	43 (24–54)‡	6 (4–10)	6 (3–23)	3 (3–8)
Placebo	3 (3–6)	3 (3–12)	3 (3–22)	3 (3–5)	3 (3–10)
Serum Somatomedin-C,† μ/mL					
BSHGH	0.66 ± 0.14	0.68 ± 0.11	1.06 ± 0.18‡	1.29 ± 0.18‡	0.64 ± 0.17‡
Placebo	0.65 ± 0.13	0.49 ± 0.11	0.34 ± 0.08	0.37 ± 0.13	0.30 ± 0.08
Serum insulin,† (μmol/mL)					
BSHGH	29 ± 6	123 ± 50‡	81 ± 21	69 ± 19	34 ± 6
Placebo	28 ± 15	38 ± 9	30 ± 9	23 ± 6	27 ± 9
Blood glucose,† mg/100 mL (mmol/L)					
BSHGH	104 ± 10 (5.8 ± 0.6)	214 ± 34 (12.0 ± 1.9)‡	190 ± 30 (10.6 ± 1.7)	164 ± 30 (9.2 ± 1.8)	102 ± 7 (5.7 ± 0.4)
Placebo	97 ± 6 (5.4 ± 0.3)	142 ± 1 (7.9 ± 1.2)	124 ± 10 (6.9 ± 0.6)	133 ± 15 (7.4 ± 0.9)	121 ± 12 (6.7 ± 0.6)

* Median (range).

† Mean ± SEM.

‡ Different from placebo, $p < 0.05$.

intake was necessary for growth hormone to produce a nitrogen sparing effect; but more recent data from Manson and Wilmore,[17] obtained from studies on healthy human subjects receiving hypocaloric intravenous feeding, have refuted this. They have demonstrated that with an intake of 1070 kcal/d and 11.3 g N/d growth hormone improves nitrogen retention and increases fat oxidation. The results of this study indicate that growth hormone can alter metabolism with minimal (400 kcal/24 h) (1675 kJ/24 h) nutritional intake.

Nitrogen balance is an index of net whole body protein balance. If whole body nitrogen turnover is measured, nitrogen intake and excretion can be used to derive rates of whole body protein synthesis and breakdown.[16] The ^{15}N from glycine has been shown to be widely distributed among the other amino acids,[18] and although growth hormone has been shown to decrease the plasma level of most amino acids[19] there does not appear to be a specific effect on glycine metabolism. In the absence of evidence for a specific metabolic pathway between glycine and urea (which is affected by growth hormone to produce a decrease in transfer of the amino nitrogen of glycine to urea), the decrease in ^{1} N enrichment of urinary urea from which the increase in nitrogen turnover with growth hormone is derived is interpreted as being an effect on whole body protein metabolism and not a specific effect of growth hormone on glycine metabolism.

The improved nitrogen balance seen with administration of growth hormone occurs with a postoperative protein synthesis rate of 209% of the corresponding synthetic rate for placebo and a breakdown rate of 170% of placebo, indicating a relative increase in synthesis to breakdown of 39%. In the absence of exogenous protein intake, the amino acids for protein synthesis will be derived from breakdown and the expression of synthesis as a percentage of breakdown will give a value for the recycling of protein and, hence, the efficiency of protein metabolism. After operation there was a decrease in recycling of protein of 12% compared with before operation in the placebo group and an increase of 5% with growth hormone, there being a 17% improvement in the efficiency of protein metabolism after surgery when growth hormone is given.

The diversion of amino acids as potential gluconeogenic substrates from oxidative to synthetic pathways when growth hormone is given results in a reduction of a mean of 51 kcal/d (214 kJ/d) derived from protein oxidation. The increased energy production of 264 kcal/d (1105 kJ/d) from fat oxidation is in excess of that required to compensate for the shortfall from protein oxidation by a mean of 213 kcal/d (892 kJ/d). It is likely that this excess in oxidation of fat is a result of the specific action of growth hormone on increasing lipolysis and free fatty acid oxidation.[19] This is seen as an overall increase in energy expenditure, most notably in the last 4 days of the study.

A diabetogenic effect of growth hormone producing increases in blood glucose and serum insulin has been described[19] and is confirmed in this study. Serum levels of growth hormone, somatomedin-C, and insulin were all affected by growth hormone administration. Growth hormone stimulates secretion of somatomedin-C from the liver[20] and the gradually increasing levels of somatomedin-C during growth hormone administration suggest a direct action of growth hormone. Insulin levels are highest when blood glucose peaks and decreases as the glucose levels fall, suggesting that insulin levels are not primarily affected by growth hormone administration but relate to the blood glucose level. Because both somatomedin-C and insulin are capable of increasing rates of protein synthesis it is not possible to determine in this study if the elevated levels of either hormone, or growth hormone itself, are responsible for the raised rate of protein synthesis.

These studies were designed to investigate the effect of growth hormone administration on postoperative metabolism and have clearly demonstrated improved protein economy and increased fat oxidation in patients with minimal nutritional intake. The suggestion that somatomedin-C is a mediator of the protein responses is worthy of further investigation; however, this will only be possible if somatomedins can be synthesized and produced in sufficient quantites by recombinant DNA technology. This study has not specifically studied clinical outcome but it is unlikely that this will be affected by these metabolic changes. The importance of the data obtained here is to provide information that can be used to evaluate the effect of growth hormone on nutrient (particularly intravenous) utilization in not only producing more efficient use of expensive materials but perhaps in reducing the quantities of nutrients that require administration, thus allowing greater use of peripheral (as opposed to central) vein feeding.

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Digital Ischemia as a Manifestation of Malignancy

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The association of malignancy with thrombotic disorders of the arterial and venous systems is well described. To date, however, there are only 23 published case reports of digital gangrene associated with malignancy. During a prospective evaluation of over 700 patients with finger ischemia, there were five patients with finger gangrene associated with malignancy. Detailed clinical and laboratory evaluation, including detailed immunologic survey and hand angiography, allowed establishment of the precise mechanisms responsible for vascular occlusions in each patient. Three mechanisms were identified: arteritis, hyperviscosity, and hypercoagulability. Digital gangrene associated with malignancy is a rare condition, the mechanism for which can be deduced by careful diagnostic evaluation.

THE OCCASIONAL ASSOCIATION of diseases of the vascular system with systemic neoplasia has been recognized for over a century. The earliest reported paraneoplastic syndrome involving the vascular system was Trousseau's description in 1865 of femoral vein thrombosis, which he termed phlegmasia alba dolens, and occult carcinoma.[1] Venous thrombosis associated with carcinoma has been reported subsequently, frequently being termed "thrombophlebitis migrans."[2–4]

Descriptions of the remote effects of neoplasms on the arterial system have increased in frequency and variety in the past several decades.[5,6] Hairy cell leukemia has been associated with classic polyarteritis nodosa.[7] Symptoms of central nervous system granulomatous angiitis have preceded the diagnosis of Hodgkin's disease in at least several patients.[8,9] Johnson et al.[10] have described vasculitis involving nutrient arteries of nerves, which may explain the frequently observed relationship of mononeuritis monoplex with small cell carcinoma and lymphoma. Ischemic tissue necrosis, possibly caused by hyperviscosity, has been reported in a patient with chronic granulocytic leukemia.[11] Cryoglobulinemia and multiple myeloma associated with Raynaud's syndrome were reported as early as 1933.[12,13]

The coexistence of digital ischemia and carcinoma was first reported in 1884 by O'Connor. He described a middle-aged woman with breast cancer and presumed left supraclavicular metastases who had gangrenous fingertips.[14] Seven years later, Fagge and Pye-Smith described a young woman with digital ischemia who was found to have a locally infiltrating tumor mass involving the first dorsal sympathetic nerve at necropsy. The patient died within 1 year of onset of symptoms. The authors hypothesized that the digital ischemia was caused by local tumor invasion or metastases to the cervical sympathetic trunk.[15]

To our knowledge there have been 23 published case reports linking digital ischemia and malignant disease. The ischemic changes have been generally bilateral, symmetric, and have involved the upper extremities. Most of the reports have described single patients, with variable, usually sparse, accompanying laboratory data. These reports are summarized in Table 1.

In the past 15 years during a prospective evaluation of over 700 patients with upper extremity ischemia, we found five patients to have finger gangrene occurring in association with systemic malignancy. Each of these patients had detailed evaluation, including magnification

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TABLE 1. *Case Reports Associating Digital Ischemia with Malignancy*

Case #	Date	Author	Sex	Age	Malignancy Type	Symptoms	Course
1	1866	Fagge and Pye-Smith[15]	F	"young"	CNS metastases, 1st dorsal nerve and sympathetic trunk metastases	Blue, cold, painful fingers	Died within 1 year
2	1884	O'Connor[14]	F	"middle aged"	Breast carcinoma	Gangrene: fingertips	Left supraclavicular metastasis
3	1901	Pasteur and Price-Jones[33]	M	61	Gastric carcinoma	Cold, blue extremities, Raynaud's	?
4	1920	Hamilton[34]	M	54	Esophageal carcinoma	Typical Raynaud's syndrome	?
5	1928	Bennett and Poulton[23]	M	61	Occult gastric carcinoma	Raynaud's syndrome	Died during cervical sympathectomy
6	1961	Domz and Chapman[27]	F	56	Adenocarcinoma right lung, myelofibrosis, cryoglobulins	Digital ischemia, gangrene fingertips	Symptoms resolved with tumor resection
7	1963	Nielson and Petri[24]	F	77	Colon carcinoma, cervical sympathetic and stellate ganglion metastasis	Symmetrical gangrene: fingers	Died
8	1959	Hawley et al. (1967)[35]	F	59	Anaplastic carcinoma of maxillary antrum	Painful, numb, gangrene digits	Died in 4 months
9	?	Hawley et al. (1967)[35]	F	54	Hypernephroma	Cold, numb, painful fingers	Return of pulses, healing of lesions, died within months
10	1964–1965	Hawley et al. (1967)[35]	F	45	Rectal/colon carcinoma, cystic ovarian tumor	Raynaud's syndrome	Died within 11 months of symptoms despite tumor resection
11	1957	Hawley et al. (1967)[35]	F	45	Adenopapillary ovarian carcinoma with metastasis	Numb, cold hands	Radiation therapy, symptoms resolved
12	1965–1966	Hawley et al. (1967)[35]	F	58	Pancreatic/ovarian carcinoma	Pain, numb, pallor: fingers	Died in 8 months
13	1953–1954	Hawley et al. (1967)[35]	F	42	Hodgkin's disease	Pain, tingling, blue fingers	Chemotherapy, radiation
14	1965–1967	Friedman et al.[25]	F	32	Epidermoid carcinoma, cervix, stage 1, ankylosing spondylitis	Raynaud's syndrome, right leg gangrene upper extremity	Symptoms improved with excision and radiation therapy
15	1966	Friedman et al.[25]	F	57	Anaplastic breast carcinoma with nodes	Ischemia and gangrene fingers and feet, bilateral thigh amputation	Symptoms resolved 22 months after mastectomy
17	1970	Powell (1973)[36]	M	7	Acute lymphocytic leukemia	Raynaud's syndrome	Remission of symptoms after chemotherapy and radiation therapy
18	1974	Palmer and Vedi[6,37]	F	62	Reticulum cell sarcoma	Finger cyanosis, bilateral splinter hemorrhages	Death months after onset of symptoms
19	1974	Palmer and Vedi[6,37]	F	74	Intra-abdominal carcinoma	Numbness, tingling and cyanosis bilateral fingers	Death months after onset of symptoms
20	1974	Palmer and Vedi[6,37]	F	66	Gastric carcinoma	Cold, blue fingers	Symptoms resolved after resection
21	1976–1977	O'Donnell et al. (1980)[28]	M	9	Acute myelocytic leukemia	Foot necrosis 9/76	Died 11/77: right main pulmonary artery thrombus
22	1978–1977	O'Donnell et al. (1980)[28]	M	52	Poorly differentiated adenocarcinoma, Buerger's disease	Claudication, great toe necrosis, brachial artery thrombosis	Died 1/79
23	1983	Wytock et al.[38]	F	59	Adenocarcinoma of ileum	Digital ischemia	Resolution of symptoms, resection × 5 years

hand arteriography and skin biopsy in three of the five patients and detailed laboratory screening for collagen vascular disease and coagulation abnormalities in all five patients. Our experience with the diagnosis and management of these patients forms the basis for this report.

TABLE 2. *Laboratory Tests for Patients with Severe Digital Ischemia*

Complete blood count
Prothrombin time
Partial thromboplastin time
Sedimentation rate
Hepatitis B antigen/antibody
Serum protein electrophoresis
Immunoglobulin electrophoresis
Rheumatoid factor
Antinuclear antibody
Extractable nuclear antigen
Raji cell immune complex assay*
Complement (C3, C4, C19 binding assay)
Anticardiolipin antibody*
Platelet count
Serum triglycerides
Serum cholesterol
Blood viscosity
Urine protein
Cold agglutinins
Cryoglobulin
Cryofibrinogen
Anti-DNA

* Not routinely obtained.

Diagnostic Evaluation

Our approach to the diagnostic evaluation of patients with severe finger ischemia is standardized and has been previously reported.[16–19] Each patient has had pharmacodynamic magnification hand arteriography and/or noninvasive digital vascular examinations to identify and quantitate digital arterial obstruction and/or vasospasm. Biopsy specimens of affected tissue were obtained for routine histologic examination and immunofluorescent staining. In addition, a standard panel of laboratory tests as outlined in Table 2 was obtained.

Case Reports

Case 1

This 53-year-old woman had a history of 11 years of episodic digital color changes with cold exposure. There was a family and personal history of neurofibromatosis, with multiple skin lesions having been removed. There was no history of collagen vascular disease. She was found to have a large fixed breast mass and had modified radical mastectomy with postoperative irradiation. Pathologic examination showed an infiltrating ductal carcinoma with 15 of 21 nodes positive. The patient's digital ischemic symptoms worsened and gangrenous lesions of multiple fingers developed. Complete serologic evaluation including antinuclear antibody, rheumatoid factor, immunoglobulin electrophoresis, complement determination, cold agglutinins, and cryoglobulins were normal. Arteriography showed numerous digital artery occlusions with associated cold-induced vasospasm. Treatment with guanethidine gave some symptomatic relief. She had persistent digital ischemia for 2 years at which time she was found to have abdominal metastatic disease and was treated with hormonal therapy and chemotherapy. She died 7 months later of metastatic disease.

Case 2

A 49-year-old woman noted the onset of bilateral finger pain and cyanosis at the time of a modified radical mastectomy for infiltrating ductal carcinoma. No axillary lymph node involvement was present. The symptoms continued for 6 months, associated with progressive digital dysesthesia and fingertip gangrene. An arteriogram showed occlusion of most named palmar and digital arteries with associated vasospasm. The digital ischemia improved slightly after brachial artery injections of tolazoline and reserpine. Chest x-ray showed pulmonary metastases, and chemotherapy was begun. The digital ischemia persisted but did not worsen. Serologic tests showed a low-titer antinuclear antibody and nonspecific mild immunoglobulin elevations. Upper extremity nerve conduction showed diffuse neuropathic changes. The patient died 2 months after the initiation of chemotherapy. At necropsy she was found to have extensive metastatic carcinoma to the viscera. Pathologic examination of the radial artery and involved skin showed no evidence of inflammatory vasculitis, immune deposits, or thrombosis.

Case 3

This 75-year-old man with a life-long history of mild, stable Raynaud's syndrome was found to have chronic lymphocytic leukemia (CLL) in 1977. He received chemotherapy and was in remission. Five years later he had an abrupt onset of blanching of both hands and feet, followed in several days by gangrenous changes of most toes and fingers. These lesions persisted despite treatment with antibiotics, corticosteroids, and pentoxifylline. A skin biopsy specimen showed lymphocytic infiltration, believed to be secondary to his CLL. He was treated with Leukeran® for 6 months and the digital lesions healed. Four months later ischemic finger lesions again developed. Evaluation revealed an exacerbation of the leukemia, with a leukocyte count of 120,000/μL and gangrene of multiple fingertips. Digit plethysmography showed decreased pulsatile flow to the affected digits. The only abnormal laboratory finding was a small amount of plasma cryofibrinogen. His evaluation is summarized in Tables 2 and 3. The digital lesions improved somewhat with the initiation of leukemia chemotherapy, but the patient died 3 weeks later of septic complications.

Case 4

A 63-year-old woman noted the precipitous onset of cold-induced tenderness and blanching of her fingers followed by cyanosis and rubor. Within 3 weeks, small ulcerations and gangrenous changes of the tips of the thumbs, index, and middle fingers of the right hand and the index and middle fingers of the left hand developed. Magnification hand angiography showed widespread palmar and digital arterial obstruction (Fig. 1). The abnormal findings of her evaluation are summarized in Table 3, and included a striking elevation of IgG to 2,800 mg/dL. Hematuria led to renal angiography, which revealed an avascular mass in the upper pole of the left kidney. A radical nephrectomy was done and the mass was found to be a sarcomatoid renal adenocarcinoma, with metastasis to hilar, periaortic, and mesenteric nodes. After operation the digital ischemia improved with healing of the lesions over the next 2 months, associated with a decrease of IgG to normal levels. She received a short course of chemotherapy. Over the next 3 years she continued to have Raynaud's attacks and recurrent digital ulcerations. She had no evidence of metastases at this time, although the carcinoembryonic antigen (CEA) remained elevated. She was treated medically for her Raynaud's syndrome. She returned 3 months later with a large epigastric mass and died soon thereafter of recurrent tumor.

Case 5

A 43-year-old man was found to have gastric adenocarcinoma with extension to regional nodes and hepatic metastases. He was treated with chemotherapy with 5-fluorouracil and developed lower extremity deep vein thrombosis. He was anticoagulated with heparin followed by warfarin. Six months later while therapeutically anticoagulated with warfarin, right axillary vein thrombosis developed followed by the rapid onset of hand ischemia progressing to gangrene of the right thumb, index, middle, and ring fingers. Digit plethysmography confirmed absent arterial flow in these four fingers with preservation of normal pulsatile flow in the fifth finger and normal palpable radial and ulnar pulses (Fig. 2). Ten days later despite heparin treatment, deep

TABLE 3. *Summary of Clinical Courses of Described Patients*

Case Number	1	2	3	4	5
Malignancy	Breast, infiltrating ductal	Breast, infiltrating ductal	Chronic lymphocytic leukemia	Renal adenocarcinoma	Gastric carcinoma
Metastases	15 of 21 axillary nodes, ovarian, iliac, mesenteric nodes	0 of 14 axillary nodes, pulmonary metastasis	Remission 1977–1982	Recurrent peritoneal nodes	Mediastinal and lymphatic metastases
Treatment	L MRM 1969 XRT 1969 Oophorectomy 1976 XRT/CTX 1976	R MRM 1983 CTX 1984	Chlorambucil CTX-1977 Chlorambucil 1982–1985 CTX 1985	L radical CTX 1974	Laparotomy, CTX
Smoking history	80 pack years	Moderate, none 1980	80 pack years, none since 1966	Unknown	>100 pack years
Associated diseases	Neurofibromatosis	None	None	None	None
Previous Raynaud's syndrome	11-year history cold-induced pain and cyanotic changes	None	Cold-induced pain and blanching since adolescence	None	None
Digital lesions	Ulcerations, cyanosis and gangrenous changes over multiple fingers (bilateral)	Dysesthesias and punctate ulcerations and several gangrenous areas over 7 fingertips	Purpura, ulcerations with gangrenous lesions over 19 fingers and toes	Ulcerations and gangrenous changes over 5 fingers (bilateral)	Gangrene of fingers and distal palm
Angiography	Multiple digital artery occlusions, marked vasoconstriction with ice immersion, relieved with reserpine	Bilateral radial artery occlusion with multiple digital artery occlusions; some improvement with tolazoline	Not done	Left hand multiple arterial irregularities with narrowing, no improvement with reserpine	Not done
Skin biopsy	Not done	No cutaneous vasculitis or inflammation (at autopsy)	1. Vasocentric lymphohistiocytic infiltrate 2. Discoid lupus V. chilblains	Mild leukocytoclastic angiitis	No arteritis, widespread venous and arterial thrombosis
Treatment of digital lesions	Good response to reserpine orally and intra-arterial	Some relief with intra-arterial reserpine/ tolazoline/ dextran IV; mild relief with nifedipine and prednisone	Initial relief with chlorambucil, local wound care and CTX with recurrence	Increased symptoms following initial slight relief with guanethidine and phenoxybenzamine with recurrence	Amputation
Outcome	Died with extensive metastases 1976	Died of septic complications of CTX for pulmonary metastasis 1984	Died of septic complications of CTX 1985	Died with recurrent tumor 1977	Died 2 months after diagnosis
Autopsy	Extensive abdominal metastases	Metastases to lung and liver, radial artery patent, no evidence of vasculitis	Not done	Not done	Not done
Outcome of digital lesions	Acrocyanosis and several ulcerations at time of death	Acrocyanosis, petechiae, and single gangrenous ulcer	Great improvement and healing of ulcerations	Painful red hands with minimal ulcerations	No new lesions

MRM = modified radical mastectomy.
XRT = radiation therapy.
CTX = chemotherapy.

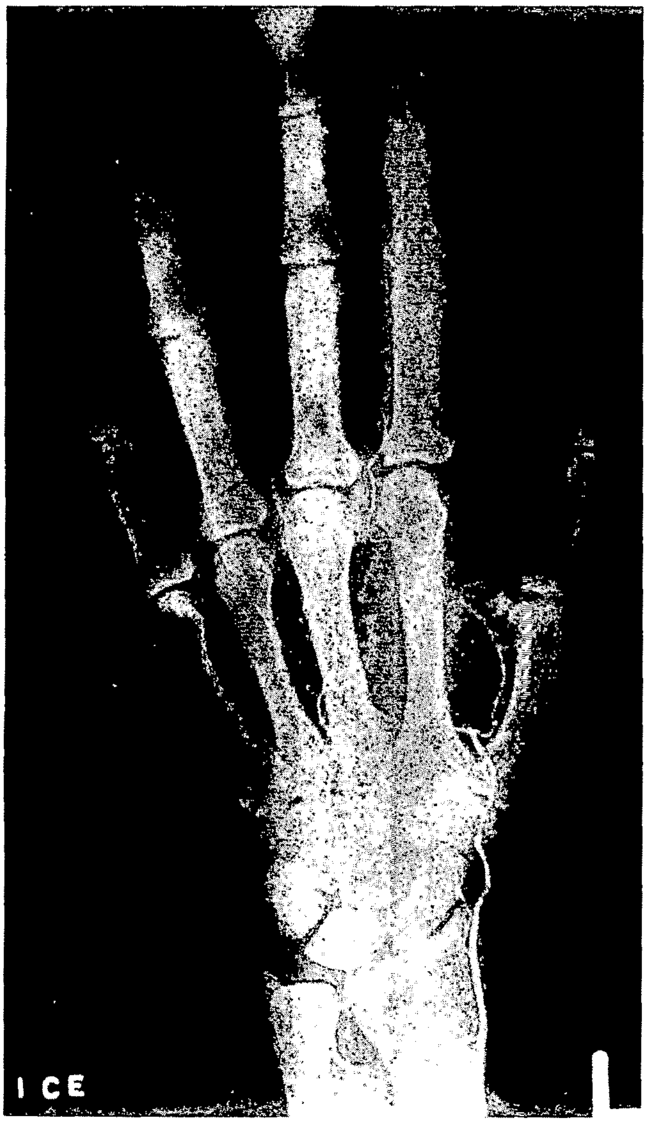

FIG. 1. Magnification hand arteriogram demonstrating widespread palmar and digital arterial obstruction (Case 4).

vein thrombosis recurred in the right leg. The patient died 2 months after limited hand amputation. Pathologic examination of the involved arteries showed no evidence of vasculitis. The details of the case histories are summarized in Table 3.

Discussion

Patients with episodic digital ischemic syndromes have been classically said to have Raynaud's disease if the condition exists alone and Raynaud's phenomenon if the ischemic symptoms exist in the presence of an associated disease process, frequently collagen vascular diseases.[20] Since neither of these terms describes a specific diagnosis, many authorities have abandoned them in favor of the term Raynaud's syndrome, used to describe the symptom complex of episodic digital ischemia in response to cold or emotional stimuli.[16] Fixed digital ischemic symptoms including gangrenous changes do not constitute Raynaud's syndrome as currently defined. Clearly, however, patients with severe digital ischemia may also have episodic symptoms that are properly termed Raynaud's syndrome. The patients described in this report all reported symptoms of Raynaud's syndrome accompanying their severe digital ischemia, and in two of the patients (Cases 1 and 3) these symptoms preceded the development of severe digital ischemia by years. The relationship between fixed digital arterial obstruction and Raynaud's syndrome has been described previously.[16]

Patients with Raynaud's syndrome may be conveniently divided into two groups, which we have termed spastic and obstructive with the differential point being the presence of fixed obstruction to flow in the palmar and digital arteries. Patients with spastic Raynaud's syndrome have symptoms as a result of an exaggerated vasospastic response to cold or emotional stimuli. Patients with obstructive Raynaud's syndrome have symptoms

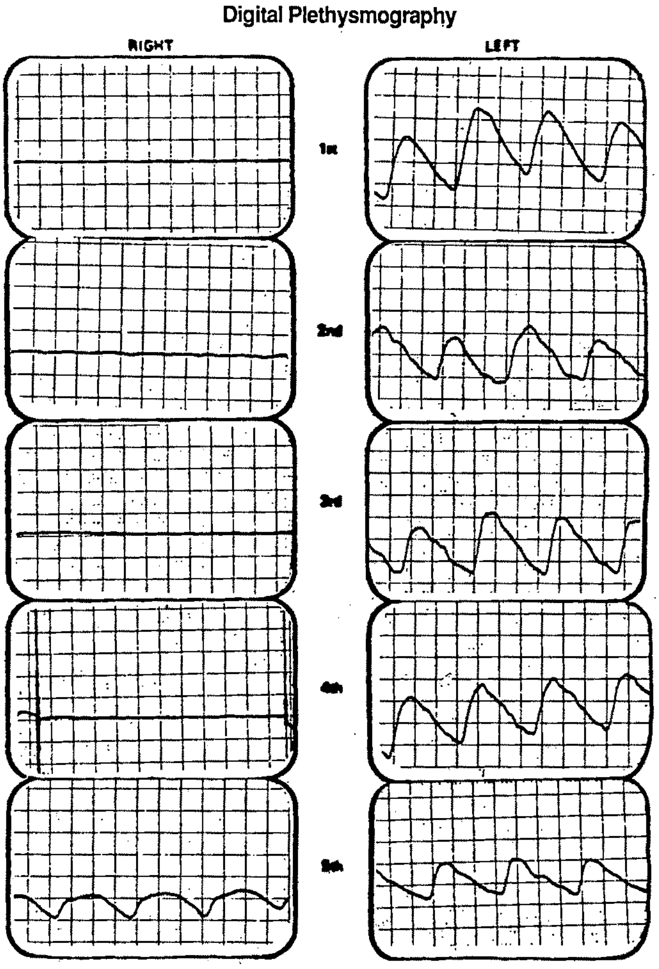

FIG. 2. Digital plethysmography demonstrating absence of pulsatile flow in right hand fingers 1–4 with normal pulsatile flow in left hand fingers (Case 5).

from digital artery closure caused by a normal vasoconstrictive response acting on an obstructed vessel.[21] Although spastic Raynaud's symptoms may be symptomatically severe, it has never in our experience caused digital gangrene. The latter has occurred only in the presence of diffuse palmar and digital arterial fixed obstructive disease.[17] The five patients with digital gangrene described in this report all had extensive fixed arterial obstructive disease in the hand and finger arteries as demonstrated by arteriography in three patients and digital plethysmography in the remainder. Three patients had a history of Raynaud's syndrome before the development of digital gangrene, and each patient had moderate improvement of ischemic symptoms after intra-arterial injection of vasodilators. Spastic Raynaud's syndrome preceding by years the development of fixed arterial obstruction and digital gangrene has been repeatedly noted by us and by others.[16,17,22]

Previous observers have postulated multiple mechanisms to explain the digital vasospasm and the digital artery obstruction producing digital ischemic symptoms in association with malignancy. Vasospasm has been attributed to sympathetic hyperactivity and to arteritis. Arterial obstruction has been attributed to arteritis, to hyperviscosity caused by elevated levels of a variety of serum proteins or of the formed elements of the blood, and to hypercoagulability associated with malignancy.

The earliest reports of digital ischemia associated with malignancy hypothesized vasospasm caused by metastatic tumor invasion of sympathetic nerves. Bennett and Poulton described in 1928 the case of a 61-year-old man with an occult gastric carcinoma who died during a cervical sympathectomy for relief of digital ischemic pain.[23] In 1963, Nielson and Petri reported a 77-year-old woman with bilateral digital gangrene and occult colon cancer with metastases to the cervical sympathetic chain and stellate ganglion.[24] None of the five patients described in this report had metastases detected to the sympathetic nerves to the upper extremity. The existence of bilaterally symmetrical symptoms in four of our five patients and in 22 of the 23 patients listed in Table 1 likewise mitigates against a local infiltrative process as the cause of this syndrome.

Arteritis of diverse etiologies has been clearly associated with digital artery vasospasm, as well as with digital artery obstruction producing finger ischemia and finger gangrene.[16,17,25] Several of the existing reports of tumor-associated digital ischemia have noted changes consistent with arteritis in the affected vessels, occasionally in association with circulating immune complexes.[26] The cause of the arteritis is unknown but may be related to tumor antigen–antibody complexes with subsequent complement activation in contact with the arterial wall.

Viscosity abnormalities have also been proposed as a mechanism of ischemia. An increase in blood viscosity may result from an increase in numbers of circulating blood cells as was noted by Hild and Myers who reported a case of ischemic necrosis of the fingertips, which they attributed to a severely elevated whole blood viscosity (Oswald viscosity: 7.1) in a patient with chronic granulocytic leukemia.[11] This mechanism appears to have resulted in digital ischemia in Case 3 in this series, in whom the granulocyte count was elevated to 120,000/μL at the time of severe symptoms. Hyperviscosity may also be caused by an increase in circulating blood proteins as was described by Domz and Chapman who related the 1961 case of a 56-year-old woman with adenocarcinoma of the lung who had elevated cryoglobulin levels and "pseudo-Raynaud's disease" progressing to gangrene. Tumor resection and concommitant decrease in circulating cryoglobulin level was associated with healing of the digital lesions and resolution of pain. Cryoglobulins were postulated to produce localized thrombosis and eventual infarction by precipitating prothrombin and accessory clotting factors.[27]

Hyperviscosity caused by cryoglobulinemia and arteritis may coexist.[28] In Case 4 described in this report, cryoglobulinemia was present in association with severely elevated IgG levels during the period of maximal digital ischemia. In this case the ischemia resolved and ulcerative lesions healed after resection of a sarcomatoid renal adenocarcinoma. Elevated gamma-globulin level, IgG immunofluorescence of tumor cells, and electron-dense deposits lining the endothelium of the tumor microvasculature were seen, suggesting the presence of immune complex deposition in vessel walls. Moore and Cupps in their review of the neurologic complications of vasculitis postulate immune complex deposition as the cause of both hypersensitivity vasculitis and systemic necrotizing vasculitis.[8] They cite the isolation of soluble immune complexes in experimental models, microscopic demonstration of immunologically mediated vascular destruction, and resolution of findings with immunosuppressants as justification for their conclusions.

Hypercoagulability in the absence of arteritis or hyperviscosity has been detected in 50–90% of patients with malignant tumors, especially those with metastases.[29,30] In as many as 15% of these patients, thrombotic events may be clinically apparent.[31] Case 5 described in this report had widespread venous and arterial thrombosis that progressed rapidly despite anticoagulant therapy. The relative resistance to treatment of this form of hypercoagulability has been well described.[32]

The fixed digital artery obstruction in these patients appeared to be caused by hyperviscosity in two patients. Arteritis was documented by pathologic findings and presumably caused the obstruction in two additional patients. In the final patient, diffuse digital artery obstruction resulted from thrombotic occlusion caused by hypercoagulability.

Four of the five patients described in this report had considerable symptomatic improvement after treatment directed at their primary neoplasms, emphasizing the ability of the hands and fingers to recover from severe ischemia, presumably through the development of collateral arterial channels.[17] Although antitumor therapy is of primary importance in treatment of these patients, the administration of vasodilators, currently calcium channel blockers, may result in moderate symptomatic improvement in those patients with an underlying vasospastic component in addition to the fixed arterial obstruction.

Digital gangrene in association with malignancy, although uncommon, is not rare and is being recognized with increasing frequency. The judicious application of angiography and plethysmography, serologic testing, and biopsy should permit accurate definition of which mechanism(s) of ischemia is (are) most important in the individual patient and permit selection of optimal therapy.

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Gastric Transposition for Esophageal Replacement in Children

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Esophageal replacement by total gastric transposition was performed on 34 infants (32 with esophageal atresia) in the 5.5-year period from January 1981 to June 1986. There were three deaths (9%), two occurring in the early postoperative period, with the third occurring 1 year after surgery from persistent chronic respiratory problems. Fourteen infants had a totally uncomplicated course and have not required further admissions. Thirteen infants had early postoperative problems including six with delayed gastric emptying, four with anastomotic strictures requiring dilatation, and two with radiologic anastomotic leaks. Four late complications consisted of two adhesion intestinal obstructions, a perforation related to a jejunal feeding tube, and a child in whom malabsorption subsequently developed. An excellent result has been obtained in 24 infants, four doing well with only minor problems with feeding, and two are fair experiencing persisting difficulties. These results compare favorably with a large previous experience in colon interposition.

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ESOPHAGEAL RECONSTRUCTIVE SURGERY presents a continuing challenge to the pediatric surgeon. The decision to replace the esophagus is always difficult due to the technical problems and major postoperative complications that may be associated with the substitution procedures. Various methods of esophageal substitution have been attempted, using either vascularized colon or jejunal interposition, gastric tubes, total gastric transposition, or free revascularized intestinal grafts to restore intestinal continuity.[1]

The significant morbidity associated with a large experience in colonic interposition at this hospital prompted a change in approach to evaluate the technique of total gastric transposition.[2] The utilization of stomach to restore continuity to the alimentary tract has been used successfully in adults for many years[3] with small reports of its use in children also being encouraging.[4,5]

This paper presents a review of the first 34 cases of transhiatal gastric transposition *via* either the posterior mediastinum or posterior thorax that have been performed at the Hospital for Sick Children in London in the 5.5-year period from January 1981 to June 1986.

Materials and Methods

Esophageal atresia was the primary condition in 32 infants with 18 having an associated tracheoesophageal fistula. In 27 infants a long gap prevented an initial primary anastomosis, whereas in five infants the initial anastomosis had disrupted and had to be abandoned. Two infants had severe esophageal damage, one from an extensive reflux stricture and the other from prolonged unrecognized foreign body impaction (Table 1).

The age at operation ranged from 7 days to 9 years with 23 of the 34 children 12 months old or less (Table 2).

Thirty-three associated congenital anomalies were identified in 13 of the 32 infants with esophageal atresia (Table 3).

Previous Surgery

Nine of the 27 infants with long gap esophageal atresia had had an initial attempt at delayed primary anastomosis. In one infant a gastric perforation developed, one infant had repeated cyanotic episodes related to upper pouch bougienage, severe aspiration penumonia developed in three infants, and in four cases the plan was abandoned as the gap did not significantly decrease after a delay of at least 60 days.

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TABLE 1. *Primary Condition in Infants with Gastric Transposition*

Condition	N
Esophageal atresia	32
Large gap + no fistula	14
Large gap + proximal TEF	3
Large gap + distal TEF	10
Failed primary anastomosis	5
Extensive reflux stricture	1
Extensive damage from prolonged foreign body impaction	1
Total	34

TEF = tracheoesophageal fistula.

Fourteen children had previous major esophageal reconstructive procedures that failed, including eight failed colon interpositions with six being referred from other institutions for esophageal reconstruction. The two children with strictures secondary to reflux and prolonged foreign body impaction, respectively, had such extensive esophageal damage that local resection and reanastomosis were not possible.

Surgical Techniques

The operative procedure consisted of either a transhiatal gastric transposition *via* the posterior mediastinum[4] without a thoracotomy in 16 infants (Fig. 1) or a thoracoabdominal gastric transposition *via* the posterior thorax in 18 children. This included the eight previously failed colon interpositions as excision of the failed colons was a hazardous procedure, especially at the thoracic inlet and root of the neck where the recurrent laryngeal nerve must be carefully identified and preserved. A thoracotomy was also considered necessary in the children with extensive esophageal strictures and some of the failed primary anastomoses where extensive scarring from the leak necessitated careful dissection to remove the esophagus.

All except one child had a gastric outlet drainage procedure with 20 children having a pyloroplasty and 13 children having a pyloromyotomy. All patients had a large calibre (12-gauge) nasogastric tube inserted to prevent postoperative gastric distension. A fine-bore jejunal feeding tube was inserted to provide enteral nutrition before oral feeding was established.

TABLE 2. *Age at Time of Gastric Transposition*

Age	N
Less than 1 month	1
1–6 months	6
7–12 months	16
13 months to 5 years	9
Over 5 years	2
Total	34

TABLE 3. *Associated Anomalies in 13 Infants*

Anomaly	N
Cardiovascular	
Patent ductus arteriosus	5
Ventricular septal defect	4
Aortic stenosis	1
Gastrointestinal	
Anorectal agenesis	4
Malrotation	3
Duodenal atresia	2
Meckels diverticulum	1
Genitourinary	
Dysplastic kidney	2
Solitary kidney	2
Hydronephrosis	1
Musculoskeletal	
Radial	2
Rib	1
Ears, nose, and throat	
Choanal atresia	2
Laryngeal cleft	1
Absent ear	1
Subglottic stenosis	1
Total	33

After operation, 25 of 34 infants were electively ventilated.

Results

There were three deaths (9% mortality rate). All occurred in children with chronic respiratory problems from previous failed reconstructive surgery. Two children had cardiac arrests within 48 hours of surgery. The first occurred in a 2.5-year-old boy with long gap esophageal atresia in whom delayed primary anastomosis failed on two occasions. He had had a tracheostomy for a laryngeal cleft and required ventilatory support for prolonged periods. The second occurred in a 1.5-year-old girl with esophageal atresia and tracheoesophageal fistula. Her initial primary anastomosis disrupted and a subsequent colon interposition failed, leaving her with severe respiratory problems.

There was one late death in a 3-year-old boy. His birth weight was 1010 g, and an attempted delayed primary anastomosis failed. He required a tracheostomy for severe aspiration pneumonia and plication of an eventuated diaphragm at 6 months of age. His chronic respiratory problems progressed and he died 1 year after a successful gastric transposition.

Fourteen children have had an uncomplicated recovery and have never required readmission for further problems. Seventeen children had one or more postoperative complications. The most frequent problem occurring in ten children involved difficulty establishing oral feeds. In six children this was due to dealyed gastric emptying. Four children responded to oral metoclopramide, whereas in two children the gastric drainage procedure required revision. In four children the feeding problems were related to an esophagogastric anastomotic stricture that resolved after dilatation. Two minor anastomotic leaks were identified on contrast radiology, which was routinely performed 7–10 days after operation. In three children respiratory distress developed after operation. In two children this was due to inefficient nasogastric tube decompression allowing the stomach to become grossly distended, compromising the ventilation. Both children rapidly responded to maneuvers to improve nasogastric drainage. In the third child, respiratory distress was due to a hemothorax from bleeding initiated in the neck during the posterior mediastinal tunnel dissection. There were four late complications. One child required a laparotomy for peritonitis from a perforation due to the feeding jejunal tube. In two children adhesion intestinal obstruction developed requiring laparotomy, and a fourth child had diarrhea with malabsorption.

After the respiratory problems experienced earlier in the series a policy of elective postoperative mechanical ventilation was adopted in the subsequent 25 infants with between 1 and 30 days of ventilatory support (mean: 4.2 days) being required. The length of hospitalization ranged from 16 to 350 days (mean: 45 days), although 18 of the 31 survivors were discharged within 30 days of surgery. The period of follow-up is from 1 month to 5.5 years (mean: 3 years).

An excellent result has been obtained in 25 children who are entirely asymptomatic and manage a normal diet. Four children are doing well with occasional minor disturbances or dysphagia. Two children have had a fair result in that although they can feed orally, they have persistent problems related to either their tracheostomies or other associated abnormalities. Although these two children have required long periods of hospitalization, they have developed normally and should eventually have a successful outcome.

Six of 23 children in whom it has been at least one year since surgery remain below the third percentile for both height and weight.

Discussion

Numerous operative procedures have been described for esophageal reconstruction in infants born with esophageal atresia. They basically involve either esophageal anastomosis with[6–10] or without elongation techniques[11,12] or abandoning the esophagus and replacing it with various substitutes.[13–17]

Esophageal preservation using delayed primary anastomotic techniques has gained acceptance for long gap esophageal atresia. This method, however, often requires many weeks of preoperative specialized nursing care with the constant threat of aspiration pneumonia developing while awaiting growth of the esophageal ends. Nine children in this series were referred for esophageal substitution having had failed attempts at delayed primary anastomosis. A significant morbidity is also associated with the subsequent procedure with reports of anastomotic leaks complicating 30–60%, anastomotic strictures in 40–75%, gastroesophageal reflux in 60%, and abnormal esophageal motility in over 70%.[18,19] In addition, the mortality rate is as high as 25–40%.[7,10,18] These results have led us to agree with other surgeons who conclude that even though anatomic repair can be achieved in nearly all patients, some would be better served by staged esophageal replacement because the prolonged attempts to elongate the esophagus may be hazardous.[19,20]

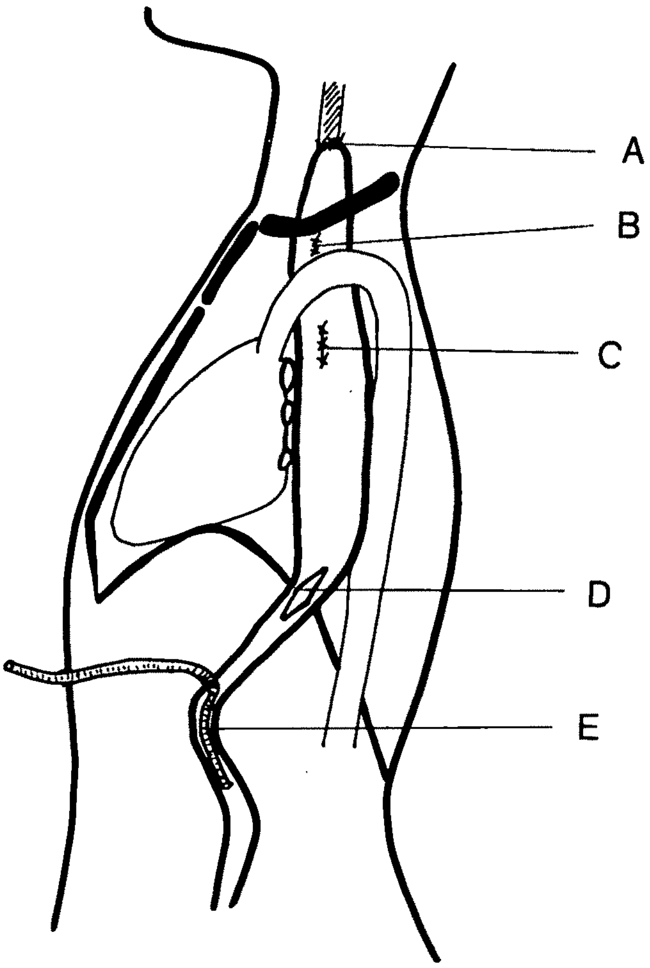

FIG. 1. Posterior mediastinal gastric transposition. A: Anastomosis of cervical esophagus to fundus of stomach. B: Oversewn junction of lower esophageal stump with stomach. C: Oversewn gastrostomy site. D: Pyloroplasty. E: Jejunal feeding tube.

Colon interposition has been widely practiced for many years as a method of esophageal replacement in

TABLE 4. *Comparison of Two Methods of Esophageal Replacement*

	Colon Interposition 1952–1981[2]	Gastric Transposition 1981–1986
Number	112	34
Mortality	13%	9%
Graft failure	14%	0%
Cervical anastomotic		
Leakage	48%	6%
Stricture	30%	12%
Outcome of survivors		
Excellent	56%	81%
Good	35%	13%
Fair	9%	6%

children.[21] It was also the approach used at this hospital until 1981 when a change was made to total gastric transposition. A comparison of 112 children who had colonic replacement of the esophagus in this hospital in the 30 years before 1981 and 34 children who had gastric transposition in the subsequent 5.5 years is summarized in Table 4.

The change to gastric transposition has resulted in a slightly lower mortality and a substantial reduction in cervical anastomotic leakage (6% *vs.* 48%) and stricture (12% *vs.* 30%). No anastomosis required revision and the strictures responded to dilatation. There were no instances of the gastric transposition failing or undergoing necrosis. Gastrointestinal bleeding, reflux, and aspiration have not been a problem. Fourteen children had a trouble-free postoperative course and no further problems have developed during the period of follow-up. The outcome for the survivors of gastric transposition also compares favorably with 81% having an excellent result against 56% for colonic interposition.

Difficulty in re-establishing oral feeds was the most common complication. The usual cause was a temporary delay in gastric emptying, although two cases in which it persisted required revision of the drainage procedure. We consider it important to perform a pyloromyotomy or a formal pyloroplasty in addition to suturing the antrum to the diaphragmatic hiatus to maintain the pylorus within the abdomen to prevent this occurrence. In another two children, a total lack of interest in oral feeding resulted in a considerable delay in their discharge. Both had been poor "sham feeders" before operation. Considerable efforts are made to ensure that all infants and parents are coping with "sham feeding" after the initial cervical esophagostomy to prevent this problem. The routine placement of a jejunal feeding tube was of great assistance to the nutritional maintenance of the children with postoperative feeding difficulties. Oral feeding can then be reintroduced as tolerated with supplementary jejunal feeds given at night.

Sixteen children did not require a thoracotomy. The distal esophagus was dissected out of the posterior mediastinum through the esophageal hiatus and a posterior mediastinal tunnel created by blunt dissection *via* the cervical incision above and through the hiatus below. A thoracotomy was considered necessary to remove a previously failed colon interposition and was preferred in cases with extensive scarring after failed primary anastomosis. The two groups of patients who had gastric transposition with or without thoracotomy were not strictly comparable because the former group tended to have had previous major surgery, whereas the latter group comprised infants with a relatively uneventful previous course. The advantages of avoiding a thoracotomy included a reduced period of postoperative ventilatory support, a lower incidence of respiratory complications, and a shorter length of hospitalization. In addition, by confining the stomach to the posterior mediastinum, the theoretical pulmonary compression caused by postprandial gastric distension is avoided (Table 5).

The period of follow-up in this series is short but almost 70% of the children who are at least 1 year post-surgery are thriving with heights and weights within the normal centiles.

TABLE 5. *Surgical Approach to Gastric Transposition*

	Posterior Mediastinum	Posterior Thorax	Total
Number	16	18	34
Postoperative ventilation (mean days)	2.5	6	4.2
Length of stay (mean days)	39	53	45
Complications	9	8	17
Deaths	0	3	3
Results			
Excellent	12	13	25
Good	2	2	4
Fair	2		2

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Results of Esophagogastrectomy for Carcinoma in Cirrhotic Patients

A Series of 23 Consecutive Patients

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Esophagogastrectomy for carcinoma of the esophagus or cardia has been performed in 23 patients with histologically proven hepatic cirrhosis. All but two patients were classified as Child's class A and all but three had a prothrombin time over 60% of normal values. Twenty-two esophagogastrostomies were performed through a separate abdominal and right thoracic approach in 15 patients, a left thoracoabdominal approach in five patients, and without thoracotomy in two patients. One patient had a colon interposition. Six patients died after operation (26%) as a result of anastomotic leakage in two patients, hepatorenal in three patients and portal thrombosis in one patient. The type of procedure did not influence mortality. The most common postoperative complication was the development of ascites (65%), and when associated with hepatorenal syndrome there was a significant mortality ($p < 0.05$). Sepsis was present in the terminal stages of all nonsurvivors. A prothrombin time less than or equal to 60% of normal values was the only significant preoperative predictive factor of mortality, with none of the three patients surviving below this level ($p < 0.05$). It is concluded that the presence of cirrhosis is not a contraindication to esophagogastrectomy for carcinoma when curative resection can be undertaken. Hepatic reserve is the determinant factor of operative prognosis. Operative risk is acceptable if patients are classified as Child's class A and prothrombin time is over 60% of normal values. Operation should be delayed when acute alcoholic hepatitis is present. Intraoperative discovery of cirrhosis is not a contraindication to resection where the above criteria are met. This strict selection allows one to anticipate a lower mortality rate.

ESOPHAGOGASTRECTOMY PROVIDES the best prospect of long-term survival[1-4] in patients with esophageal carcinoma. Patients with cirrhosis may not be considered for surgical resection because of the high mortality and morbidity rates of gastrointestinal surgery reported in such patients.[5-8] However, with the advances in surgical treatment of esophageal carcinoma, and the lower associated mortality and morbidity,[1-3,9] some patients with cirrhosis may be candidates for surgical resection. The purpose of this study is to report our experience of esophagogastrectomy in patients with cirrhosis, and through the analysis of the data, we propose selection criteria for sugical intervention in this high-risk group of patients.

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Materials and Methods

The charts of all consecutive patients with an association between carcinoma of the esophagus or cardia and cirrhosis treated in the Department of Digestive Surgery of Hopital Beaujon between January 1979 and May 1986, were retrospectively reviewed. Only those patients who had an esophagogastrectomy will be further discussed. Data concerning the history, diagnosis, and staging of both the tumor and the cirrhosis were listed for each patient. Preoperative data listed included serum levels of bilirubin, alkaline phosphatase, transaminases, and albumin. Prothrombin time was expressed as a percentage of normal values. Child's original classification[10] and prothrombin time were used to asses the severity of liver dysfunction. All patients had proven hepatic cirrhosis from preoperative and/or intraopertive liver biopsy. Pathology reports were reviewed to confirm cirrhosis and to assess the presence of stigmata of alcoholic hepatitis graded from absent to severe.[11] The location, histologic type and stage of the esophageal tumor were listed. Intraoperative data were collected including surgical procedure, operative duration and transfusion requirements. Postoperative mortality and morbidity were listed. Documented complications included: anastomotic leakage, pulmonary failure, ascites, hepatic fail-

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ure, and sepsis. Objective criteria were established defining each complication as follows: anastomotic leakage was radiologically documented by water soluble contrast swallow on postoperative day 7, or earlier in the presence of clinical symptoms of leakage; pulmonary failure was documented by abnormal chest roentgenogram showing penumonia or atelectasis, and/or the use of ventilator assistance for 4 days or more, in the absence of other major complication; ascites was documented by an increase of weight and abdominal circumference or issue of transsudative liquid through the drains; high flow ascites with renal failure defined hepatorenal syndrome; hepatic failure was defined by the association of prothrombin time below 60% of normal and a serum bilirubin level over 2 mg/dL; sepsis was documented by fever and positive cultures of ascites, sputum, blood, or urine. Length of hospitalization and survival were studied.

Operative mortality was statistically studied as a function of pre-intra-, and postoperative data by the Fisher's exact test for qualitative data and Student's t-test for quantitative data. Survival was studied by the Kaplan-Meier method.

Results

Patients

From January 1979 to May 1986, 718 patients with esophageal carcinoma were referred to our department. Hepatic cirrhosis was present in 48 patients (6.6%). Twenty-five patients were not operated on because of advanced tumors or cirrhosis. Twenty-three patients (48%) were operated on and had an esophagogastrectomy. There were 21 men and two women, aged 42–75 years (mean: 58 years).

Esophageal Tumors

Three patients had a cardioesophageal adenocarcinoma. Twenty patients had a squamous cell carcinoma: four were located on the lower third, 14 were located on the middle third, and two were located on the upper third of the esophagus. Tumors were considered to be suitable for resection on the absence of malignant spread judged on chest roentgenogram, tracheobronchoscopy, ultrasonography, computerized tomography, and isotopic bone scanning.

Cirrhosis

All patients were alcoholics and had histologically proven hepatic cirrhosis. A diagnosis of cirrhosis was made during operation in four patients. Two patients had previously had gastrointestinal bleeding from esophageal varices. In the remainder, diagnosis of cirrhosis was made during the staging of the esophageal carcinoma. Two patients were classified as class B in the Child's classification because of low albumin level (3 g%) in one patient and high bilirubin level (3 mg%) in the other; the other 21 patients were classified as class A. Three patients had a prothrombin time at 60% or less than normal values. Nine patients had normal hepatic tests. All patients were in good general condition.

Surgical Technique

All patients had an esophagogastrectomy, including 22 esophagogastric anastomoses and one colon interposition in a patient who had had a previous gastrectomy for peptic ulcer. The esophageal anastomoses were all made with an EEA or ILS stapling device. There were 19 intrathoracic anastomoses and four cervical anastomoses. Patients were classified into three groups according to the procedure used. Group 1 includes 16 patients who had esophagogastrectomy through a separate abdominal and right thoracic approach; there were 14 intrathoracic esophagogastrostomies and two cervical anastomoses through an additionnal incision. Group 2 includes five patients who had esophagogastrectomy through a single left thoracoabdominal approach. Group 3 includes two patients who had extrathoracic blunt esophagogastrectomy through an abdominal and cervical approach. Two thoracic drains were placed after all thoracotomies. All patients had abdominal drainage. Small-caliber suction drains were used. An intraoperative wedge liver biopsy was made in all patients. Mean duration and transfusion requirements in group 1 patients were 6.4 ± 1.1 hours and 2.7 ± 1.4 units, respectively; four patients died. The values were 4.2 ± 1.1 hours, 4.2 ± 0.2 hours, 1.2 ± 1.4 units, and 1.5 ± 1.5 units in groups 2 and 3, respectively. Two patients from group 2 and none from group 3 died. Operations in group 1 were longer and required more transfusions than the other groups ($p < 0.05$), but mortality was not significantly different.

Operative Mortality and Complications (Tables 1 and 2)

All patients remained in an intensive care unit for at least 8 days, with a minimum 12 hours of artificial ventilation. Postoperative care included water and sodium restriction, infusions of albumin and fresh-frozen plasma, diuretic and antibiotic therapy. Four patients had an uncomplicated postoperative course. Nineteen patients (87%) had 53 postoperative complications, and of these six died (26%). Causes of postoperative deaths were anastomotic leakage in two patients, hepatorenal syndrome in three patients, and mesentericoportal thrombosis with resultant intestinal infarction in one patient. Anastomotic leakage occurred in three patients (13%). One patient died after early disruption of the

TABLE 1. *Complications and Their Relationship with Mortality*

Complication	No. of Patients (%)	Mortality if Complication Present (%)
Anastomotic leakage	3 (13)	2 (66)
Pulmonary failure	4 (17)	0 (0)
Ascites	15 (65)	5 (33)
Hepatorenal syndrome*	3 (13)	3 (100)
Ascitic leak	3 (13)	2 (66)
Sepsis*	10 (43)	6 (60)
Hepatic failure	9 (39)	4 (44)
Portal thrombosis	1 (4.3)	1 (100)
Early wound hernia	2 (8.6)	1 (50)

* $p < 0.05$ by Fisher's exact test.

anastomosis. Two patients had small anastomotic leaks, visible on routine contrast examination, but one patient subsequently died of an empyema, whereas the other patient healed on antibiotic therapy and parenteral nutrition. The most common complication was the development of postoperative ascites. It was observed in 15 patients (65%) and was associated with five deaths (33%). Fourteen of the 15 patients with ascites (93%) had a pleural effusion similar to ascitic fluid, and its evolution paralleled that of the ascites. Mean ascitic flow estimated on drain loss was 1450 mL/24 hours (500–3000 mL). Maximum ascitic flow was observed during the 5 days after operation and progressively decreased. Four patients had persistant ascites over 2 weeks. Hepatorenal syndrome developed in three patients and they died ($p < 0.05$); they all had an ascitic flow over 2000 mL/24 hours. Among the four patients with persistant ascites, ascitic leak occurred in three patients after removal of the drains; one had an infected ascites. Sepsis was observed in 10 patients and was associated with six deaths ($p < 0.05$). Two patients had positive ascitic cultures and died, four patients had pleural positive cultures and three died, four patients had positive sputum cultures and two died, two patients had positive blood cultures and one died, and five patients had positive urine cultures and three died.

Relationship between Preoperative Status and Mortality (Table 3)

Nine patients had normal hepatic tests; none of them died. Among the 14 other patients with abnormal values, six (42%) died. The only factor that significantly influenced operative mortality was a preopertive prothrombin time at 60% or less of normal values, with none of the three patients surviving below this level ($p < 0.05$). Hepatorenal syndrome developed in these three patients.

Outcome

Mean duration of hospitalization in survivors was 25.9 ± 12.5 days. No adjuvant therapy was used. One patient had several recurrences of ascites and encephalopathy with no sign of recurrent malignancy; the other patients recovered preoperative liver function. One patient with postoperative recurrent nerve paralysis died of aspiration pneumonia 8 months after surgery. Among the 16 surviving patients nine are alive and free of disease at between 5 and 77 months; seven died of cancer with a mean survival of 17 months. The actuarial survival rate is 72% at 1 year and 27% at 3 years.

Discussion

Esophagogastrectomy for carcinoma in cirrhotic patients has been mentioned only occasionally in the literature.[3,9,12] It is well established that gastrointestinal surgery in nonbleeding cirrhotic patients carries a high risk of mortality and morbidity. Mortality rates of 20–30% have been reported.[5,6] In this study we present a series of 23 consecutive esophagogastrectomies for carcinoma in an homogeneous group of cirrhotic patients with a 26% mortality rate. This rate is much higher than the 1.5–10% mortality rate reported for esophagogastric resection in noncirrhotic patients,[1–3,9] but our results compare favorably with those reported for more minor abdominal procedures in cirrhotic patients.[7,8] Our results indicate a 6.6% prevalence of alcoholic cirrhosis in patients with esophageal carcinoma, which has not been previously reported.

In this series, several types of esophagogastrectomies have been used. Operative mortality was not significantly influenced by the type of procedure, although operations with a separate abdominal and thoracic approach (group 1) were longer and required more blood transfusions. Where tumor was located on the lower third of the esophagus, a left thoracoabdominal ap-

TABLE 2. *Operative Mortality*

Patient #	Age	Child's Class	Pr (%)	AAH	Procedure	Cause of Death
1	62	B	100	+	Group 2	Anastomotic leak, day 4
2	69	A	83	−	Group 1	Blind fistula, day 33
3	63	A	76	−	Group 2	Portal thrombosis, day 23
4	42	A	60	−	Group 1	Hepatorenal syndrome, day 33
5	57	A	57	−	Group 1	Hepatorenal syndrome, day 23
6	49	A	58	+	Group 1	Hepatorenal syndrome, day 16

Pr (%) = prothrombin time in percentage of normal values.
AAH = acute alcoholic hepatitis.
+/− = present/absent.
See text for explanation of groups 1 and 2.

proach was used (group 3) to provide a better exposure of the esophagogastric junction and the splenic hilus. In middle-third tumors we have used a separate abdominal and right thoracic approach because of the necessity of a supra-aortic anastomosis. Two extrathoracic blunt esophagectomies (group 3) were peformed with a low intraoperative blood loss for a lower and an upper third growth, respectively. The favorable outcome in our two patients contrasts with the experience of Baker and Schechter[12] who reported two deaths in these cirrhotic patients who had extrathoracic esophagectomy. In contrast to other reports,[5,6] we did not find any correlation between mortality and intraoperative blood loss, which was estimated on transfusion requirements. This is probably explained by the fact that no massive intraoperative hemorrhage occurred. Cautious dissection and hemostasis are important. Thus, we cannot recommend one type of esophagogastrectomy in these patients; the choice must depend on the location of the growth and not on the presence of cirrhosis.

Mortality and morbidity after esophagogastrectomy is usually related to anastomotic leakage and pulmonary failure.[1,3,9,13] In this series, no patient died of pulmonary failure, and the rate of anastomotic leakage is not dramatically higher than in noncirrhotic patients.[9,13]

Four of the six deaths and most of the complications were directly related to cirrhosis. Ascites occurred in 65% of the patients in our series. It is a common complication after laparotomy in cirrhotic patients.[5,14] In one patient, ascites was due to a mesentericoportal thrombosis, but in 14 patients it was a primary complication directly related to the operation. The high frequency of postoperative ascites in our series could be explained by the interruption of the peri- and intraesophageal collateral circulation and by extensive lymphatic dissection.[14] Development of postoperative ascites gives rise to concern in these patients because it may expose them to the following specific risks: leakage of ascites through drain sites or operative wound with a risk of infection of ascites,[5] wound dehiscence, diaphragmatic compression, and metabolic disorders, including hyponatremia and renal failure favored by drain loss and diuretic therapy. This latter complication is important since high flow ascites with renal failure (hepatorenal syndrome) was associated with a significantly higher mortality. Prevention of postoperative ascites is difficult, but it is best done by water and sodium restriction and careful prescription of diuretics. When it develops, ascites should be evacuated to prevent parietal and respiratory complications. The two available methods are repeated paracentesis or abdominal drainage. Abdominal drainage is usually avoided when postoperative ascites is anticipated because of the risks of ascitic leak and infection. However, in previous reports, abdominal drainage after celiotomy in cirrhotic patients has not been associated with a higher mortality rate.[5] In this series, the 15 patients in whom postoperative ascites developed had drainage with only three leaks after the drains were removed and one ascites infection. We recommend one-way suction tubes, which should be removed only after ascites has been controlled. Drain loss must be compensated by albumin and fresh-frozen plasma and clinical and biological parameters closely monitored to detect and correct metabolic disorders. A pleural effusion was almost constant in the patients with ascites; it must be considered as a manifestation of ascites due to the peritoneopleural communication created by the operation. It represents another argument for abdominal drainage. Its managment is the same as that of ascites.

TABLE 3. *Relationship between Preoperative Status and Mortality*

Variable	No. of Patients (%)	Mortality if Variable Present (%)
Child's class B	2 (8.6)	1 (50)
Pr < 60%*	3 (13)	3 (100)
AAH present	5 (21)	3 (60)
Normal hepatic tests	9 (39)	0 (0)
Intraoperative discovery of cirrhosis	4 (17)	1 (25)

* $p < 0.05$ by Fisher's exact test.
Pr < 60% = prothrombin time 60% or less of normal values.
AAH = acute alcoholic hepatitis.

Postoperative hepatic failure, as defined above, was not a significant cause of mortality. However, our criteria can be criticized since modifications in bilirubin level and prothrombin time can results from other causes in the postoperative period such as blood transfusions, anesthetic agents, and disseminated intravascular coagulation. A postoperative increase in bilirubin level and decrease in prothrombin time were associated with death only in the patients in whom hepatorenal syndrome developed; thus, the latter syndrome seems to be the most specific stigmata of postoperative liver failure.

Sepsis was a major problem in the postoperative course of our patients and was present in all nonsurvivors, but in all of them, it followed on from a previous complication. It is best prevented by a meticulous postoperative care, and major antibiotherapy seems justified. Recent data suggest that broad-spectrum cephalosporins are the antibiotics of choice.[15]

Several recent reports, such as those by Garrisson et al.[5] and Doberneck et al.,[6] have studied operative risk of abdominal procedures in nonbleeding cirrhotic patients. They all confirmed that the main preoperative predictive factor of mortality was the degree of hepatocellular insufficiency, best reflected by the Child's classification and a decrease in prothrombin time. This is also true for the Sugiura operation[16] which shows some similarity with esophagogastrectomy. It would appear that cirrhotic patients with an esophageal carcinoma must be part of the best risk class to be candidates for surgical resection. In this series, all but two patients were classified as Child's class A, and the only significant preoperative predictor of mortality was a prothrombin time less than or equal to 60% of normal values. Three patients had a prothrombin time of 60% or less; they all had development of hepatorenal syndrome and died. Two patients were classified as Child's class B and one died. In retrospect, these five patients probably should not have been operated on. A high probability of resectability is also mandatory before proposing elective surgical exploration for esophageal carcinoma in patients with cirrhosis. Thus, strict preoperative selection of the patients can improve the results; none of the six consecutive patients operated on in the last 2 years died. It is interesting to note that, although this is not significant, intraoperative discovery of the cirrhosis and normal preoperative hepatic tests were associated with a lower mortality rate (1/4 and 0/9, respectively). Patients in whom cirrhosis is discovered during operation usually have an infraclinical cirrhosis and fulfill the above criteria of operability. Thus, intraoperative discovery of cirrhosis is no contraindication to resection.

Another factor that can alter hepatic function is the presence of acute alcoholic hepatitis (AAH). Whether AAH carries a higher risk for surgery or not has been well studied for shunt procedures[11,17]; it remains a matter of argument. It seems that quantitative statement of AAH is important. In this series no patient had severe AAH, but five had mild histologic signs of AAH with a few Mallory bodies and slight degree of necrosis; none had normal hepatic tests and three died. Although these observations were not statiscally significant, we believe that AAH must be considered a temporary contraindication. Therefore, we suggest that the presence of AAH should be assessed by a preoperative liver biopsy in patients with abnormal hepatic tests.

One of our patients died of postoperative mesentericoportal thrombosis with intestinal infarction. Mesentericoportal thrombosis is not an uncommon complication in cirrhosis[18,19]; it is favored by stasis in the mesentericoportal bed due to portal hypertension. It has been reported by Sugiura as a lethal complication of his operation.[15]

No postoperative gastrointestinal bleeding was observed. This can be explained by the fact that esophagogastrectomy is the most complete devascularization, with clearance of esophagogastric varices, similar to that aimed by the Suguira-type procedures.[20]

This study shows that major surgery in good-risk patients with cirrhosis does not definitely impair hepatic function in the surviving patients. Among the surviving patients of this study, all but one recovered preoperative hepatic function. Their survival compares with that of noncirrhotic patients in whom curative resection can be attained.[1] This is probably a result of a strict preoperative staging.[1]

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Effects of Thymectomy in Myasthenia Gravis

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Factors influencing onset of remission in myasthenia gravis were evaluated in 2062 patients, of whom 962 had had thymectomy. Multivariate analysis showed that appearance of early remissions among all patients was significantly and independently influenced by thymectomy, by milder disease, and by absence of coexisting thymomas. Patients with mild generalized symptoms treated with thymectomy reached remission more frequently, even when compared with those with ocular myasthenia treated without surgery. Short duration of disease before thymectomy in mild cases was another factor associated with earlier remissions. Mortality for all patients was significantly and independently influenced by severity of symptoms, age, associated thymomas, and failure to remove the thymus. Patients without thymectomy and with thymomas had, in addition, earlier onset of extrathymic neoplasms. Morbidity after the transcervical approach was minimal. This study demonstrates that early thymectomy by the transcervical approach, when technically feasible, has significant clinical advantages over the transthoracic approach and should be advocated for all patients with myasthenia gravis, including those with ocular disease.

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THE ROLE OF THYMECTOMY in myasthenia gravis has not been fully investigated beyond confirming early empirical observations[1] that it is frequently followed by remission of symptoms of the disease. Reports of delayed remissions after thymectomy,[2,3] of decreases in associated extrathymic neoplasms,[4] and of the low morbidity with the transcervical approach[5] have provided additional indications for early surgical intervention, even in patients with mild generalized symptoms. As a result, thymectomy, which was previously used in a selected subgroup of patients,[6] is now performed in all patients with generalized disease.

Indications for the various treatment modalities have changed in recent years. Age, sex, severity of symptoms, lack of control of symptoms with medication, duration of disease, and presence of thymoma were used in earlier years as indicators for surgery.[6] The effect of these factors on the clinical course of the disease has not been adequately studied, even though they should be considered potential confounders when evaluating the results of treatment. It seemed appropriate, therefore, to perform multivariate analysis to identify factors that significantly influence the time intervals either from diagnosis or from thymectomy, to the onset of remission, the development of extrathymic tumors, and death.

The long-term results of the transcervical and transthoracic approaches were compared to determine whether the latter offers any clinical advantage, since in the existing controversy proponents of the sternal approach have advocated a "complete thymectomy" rather than demonstrating a clinical advantage from "radical thymectomy."[7-10] The immediate postoperative course of transcervical and transthoracic approaches was also evaluated.

Materials and Methods

The clinical course of 2062 patients with myasthenia gravis registered at our institution between 1951 and 1985, of whom 962 had had thymectomy, was evaluated to identify factors that influenced the onset of complete remission, the appearance of extrathymic neoplasms, and mortality.

The following factors were considered potential confounders in evaluating the interval from onset of disease, or from surgical treatment, to the end points of the study: age and sex of the patient, age at onset of symp-

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TABLE 1. *Patients in the Study*

Treatment	No Thymectomy	Thymectomy All	Thymectomy Cervical	Thymectomy Thoracic
No thymoma	1048	788	651	137
Ocular/Mild/Severe	(297/401/350)	(3/472/313)	(3/432/216)	(0/40/97)
Thymoma	52	174	44	130
Ocular/Mild/Severe	(4/11/37)	(9/57/108)	(0/22/22)	(9/35/86)
Total	1100	962	695	267

toms, severity of disease at time of confirmation of diagnosis, presence of thymoma, age at thymectomy, time period and hospital where surgery was performed, surgical technique, operating surgeon, and duration of disease from onset to thymectomy. For the development of extrathymic tumors, only the first primary malignancy, occurring after the diagnosis of myasthenia gravis, was taken into consideration. Skin neoplasms other than melanomas were not included in the analysis.

In the multivariate analysis severity of disease was coded as: ocular; mild generalized, which included cases with Classes IA and IIA symptoms; or severe, which included cases with Classes IIB, III, and IV symptoms, using the Osserman classification.[11] Duration of disease before surgery was coded as either short, *i.e.*, less than 3 years, or long, which included patients operated on with a delay of 3 or more years after diagnosis. Surgical technique was coded as transcervical or transthoracic. The latter included median sternotomy (complete or partial), lateral intercostal thoracotomy, and parasternal mediastinotomy. One of us (AEP) performed 557 operations, of which 512 were for patients without associated thymoma, and results in this group were compared with those obtained by other surgeons. Patients followed at our institution but operated on in other hospitals were grouped in a separate category. Remissions and mortality were evaluated from the time of diagnosis in all patients and also from the time of surgery in those patients who had thymectomy. Since the proportion of patients in remission increases with time after thymectomy,[2] the analysis of patterns of remission was performed taking this factor into consideration.

Postoperative mortality, need for prolonged postoperative ventilatory assistance or for tracheostomy, and length of hospital stay were factors that were considered in evaluating the immediate postoperative course. The postoperative courses of patients operated on between 1973 and 1986 were evaluated separately from those of the preceding period, as the perioperative management of patients remains essentially unchanged since 1973. Adherence to a variety of postoperative treatment protocols in different years precluded an unbiased evaluation of the immediate postoperative course and complete information on the variables of interest was not available in all patients.

Follow-up information was obtained by patient examination or by questionnaire. Statistical analysis of onset of remission, mortality, and appearance of extrathymic neoplasms was performed using the Cox Proportional Hazards model[12] and the patterns of remissions and of mortality were plotted using the 1L program of the BMDP Statistical Software package (BMDP Statistical Software, Department of Biomathematics, University of California, Los Angeles, CA).[13] Associations between noncontinuous variables were evaluated using the chi-square test.

Results

Thymectomy and/or the transcervical approach were treatment methods not evenly distributed among subgroups of patients. There were significant variations in the proportions of patients with thymomas and/or severe symptoms both among the groups treated with or without surgery and within the subgroups defined by surgical technique. Thymomas were observed in 226 of 2062 patients (11%) with myasthenia gravis. Among patients who had thymectomy, the proportion was significantly higher compared with that of patients who were not operated on as 174 of the 963 patients who were operated on (18%) were found to have thymomas, compared with 52 of 1100 (5%) patients who were not operated on ($p = 0.0001$). Significant differences in the percentage of thymomas were also noted in relation to severity of disease. Among mild cases, 81 of 1254 patients (6%) had thymomas, whereas among those with severe symptoms 145 of 808 patients (18%) had associated thymic tumors ($p = 0.0001$). Only one third of patients without thymomas had severe symptoms compared with two thirds of those with associated thymomas. The majority of patients who had thymectomy (72%) were operated on *via* the transcervical approach but there was a significant difference in this proportion in relation to the presence of thymoma. Of 788 patients without thymoma, 651 (83%) had transcervical thymectomy compared with 44 of 174 patients (25%) with thymoma ($p = 0.0001$). Most patients who had the transcervical approach had milder disease compared with those operated on by one of the transthoracic approaches (Table 1). The majority of patients with ocular disease were not

TABLE 2. *Clinical Outcome*

	No Thymectomy						Thymectomy							
Class	All	Remission (%)	Mortality (%)	Extrathymic Neoplasm			All	Remission (%)	Mortality (%)	Extrathymic Neoplasm				
Ocular I	301	59 (20)	39 (13)	(6)*	22†	8%§	12	2 (18)	2 (18)	(1)*	0†	(0)‡	0%§
No thymoma	297	58 (20)	37 (12)	(6)	21	7%	3	1 (33)	1 (33)	(1)	0	(0)	0%
Thymoma	4	1 (25)	2 (50)	(0)	1	25%	9	1 (11)	2 (22)	(0)	0	(0)	0%
Mild IA, IIA	412	64 (15)	87 (21)	(10)	41	10%	529	125 (23)	41 (7)	(9)	22	(13)	4%
No thymoma	401	63 (16)	81 (20)	(10)	40	10%	472	120 (25)	28 (6)	(8)	17	(8)	4%
Thymoma	11	1 (9)	6 (55)	(0)	1	10%	57	5 (9)	13 (23)	(1)	5	(5)	9%
Severe IIB, III, IV	387	25 (6)	159 (41)	(9)	26	8%	421	71 (17)	96 (23)		20	(12)	5%
No thymoma	350	25 (7)	129 (37)	(7)	22	6%	313	60 (19)	45 (14)	(7)	13%	(8)	4%
Thymoma	37	0 (0)	30 (81)	(2)	4	11%	108	11 (10)	51 (47)	(3)	6	(4)	6%
Totals	1100	148 (13)	285 (26)	(25)	89	8%	963	198 (21)	139 (14)	(20)	42	(25)	4%
No thymoma	1048	146 (14)	247 (25)	(23)	83	8%	788	181 (23)	73 (9)	(16)	30	(16)	4%
Thymoma	52	2 (4)	38 (73)	(2)	6	12%	174	17 (10)	66 (37)	(4)	12	(9)	7%

* Neoplasms diagnosed before onset of myasthenia gravis.

† Neoplasms diagnosed after onset of myasthenia gravis.

‡ Neoplasms diagnosed after thymectomy.

§ Percentage of patients in whom neoplasms developed after onset of symptoms.

treated by thymectomy. Remission and mortality varied significantly with severity of disease and presence of thymoma in both the operated and nonoperated groups of patients (Table 2). Overall, patients who had thymectomy had a higher proportion of remissions, lower mortality, and less frequent extrathymic neoplasms.

Severity of disease, presence of thymoma, and thymectomy were all factors that emerged from the multivariate analysis using the Cox Proportional Hazards model as significantly and independently influencing the interval from onset of disease to onset of remission. The most important factors contributing to an early onset of remission were milder forms of disease, thymectomy, and absence of thymoma with all three factors having a significant and independent influence (Table 3). Sex and age of the patient did not influence the results. The patterns of remission from time of diagnosis for patients with or without thymectomy and with or without thymoma are shown in Figure 1. The earliest remissions appear in patients without thymoma treated by thymectomy. Patients with thymomas who had operation, although they had considerable delay in onset of remissions, eventually had a higher proportion of remissions than patients without thymomas treated without surgery (Fig. 1).

The analysis was repeated in patients without thymoma after stratification according to severity of symptoms. A higher proportion of remissions was noted in those with mild disease treated by thymectomy. Patients who had progressed to severe symptoms before thymectomy had a similar pattern of remission as patients treated without thymectomy who had ocular or mild generalized symptoms. The group with the fewest remissions was that of patients who had progressed to severe symptoms but had not had thymectomy (Fig. 2). The duration of preoperative symptoms for patients who had thymectomy is shown in Table 4. It was noted that 25% of patients without thymoma had a duration of symptoms of more than 3 years by the time of thymectomy. Although 87% of thymomas were diagnosed and treated within 3 years of onset of symptoms among patients operated on in each of the subsequent periods, 21 of 218 patients (10%) were found to have thymomas (Table 4). Thymomas were found with increasing frequency in the older age group, particularly among patients with severe symptoms. The highest proportion (42%) was noted in patients over 50 years of age at the time of surgery, who had severe symptoms.

When remissions were evaluated for patients who had thymectomy, it became evident that the time from thymectomy to remission was significantly and independently influenced by the presence of thymoma, severity of disease, the surgical approach, and by the duration of preoperative symptoms. Patients without thymoma, those with milder symptoms, those who had had transcervical thymectomy, and those with short duration of disease (less than 3 years) showed earlier onset of remis-

TABLE 3. *Factors Influencing Remission After Diagnosis in all Patients**

	Univariate p	Stepwise p	Coefficient/SE
Severity of disease	0.0000	0.0000	−4.9393
Thymectomy	0.0002	0.0000	4.8537
Thymoma	0.0058	0.0130	−2.7083

* Age of onset of symptoms and sex of patient had no independent significant effect. Number of patients = 2062; number of patients in remission = 346.

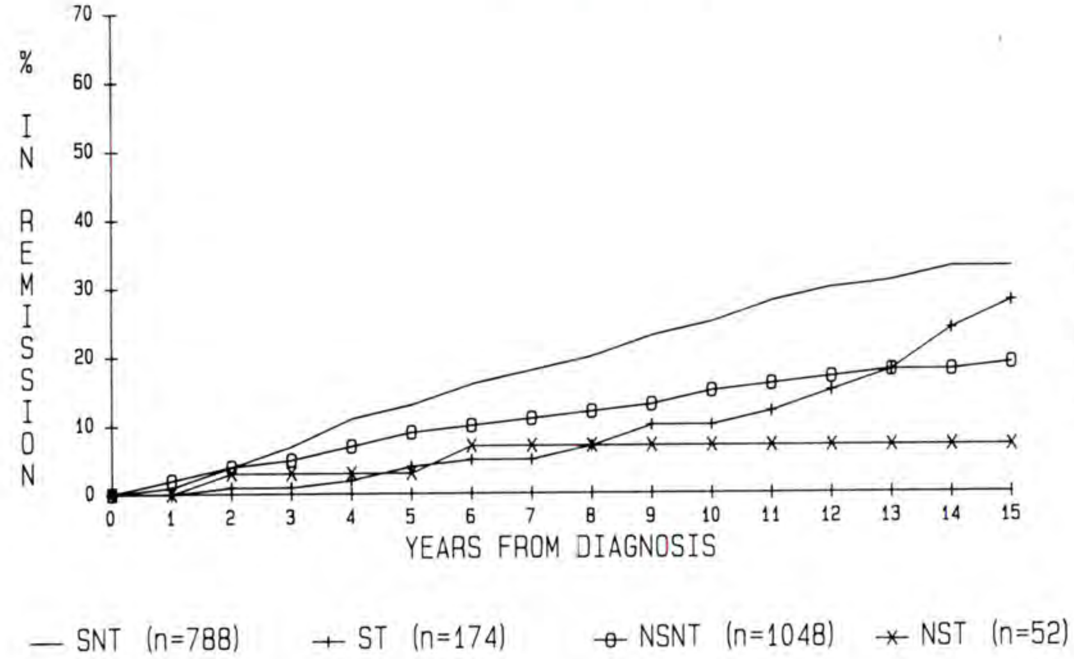

FIG. 1. Intervals from diagnosis to remission in relation to treatment and presence of thymoma. SNT: thymectomy, no thymoma; NSNT: no surgery, no thymoma; ST: thymectomy, thymoma; NST: no surgery, thymoma.

sion (Table 5). Comparison of the patterns of remission from the time of surgery in patients with and without thymoma revealed that patients without thymoma and who were operated on by the transcervical approach had earlier remissions, and the advantage was sustained in the entire follow-up period (Fig. 3). No significant difference in the remission rate of patients with thymomas was noted in relation to surgical technique.

The pattern of remissions was evaluated separately for patients operated on by one of us (AEP) because inclusion of the variable "surgeon" in the multivariate analysis showed that this factor significantly influenced the results. Within the homogeneous group of patients without thymomas who were operated on by AEP, those who presented a combination of mild disease with short duration of symptoms had the earliest onset of remissions, whereas the other three groups showed delayed patterns (Fig. 4). The analysis was limited to the first 10 postoperative years because there were no patients with mild symptoms who were operated on within 3 years from onset of myasthenia, with a follow-up longer than 12 years. At 10 years after thymectomy, 67% of patients with short duration of symptoms and mild disease were in remission compared with 28% of those who had progressed to severe symptoms.

The interval from the time of diagnosis to death of the disease was influenced significantly and independently by the factors shown in Table 6. Those patients who

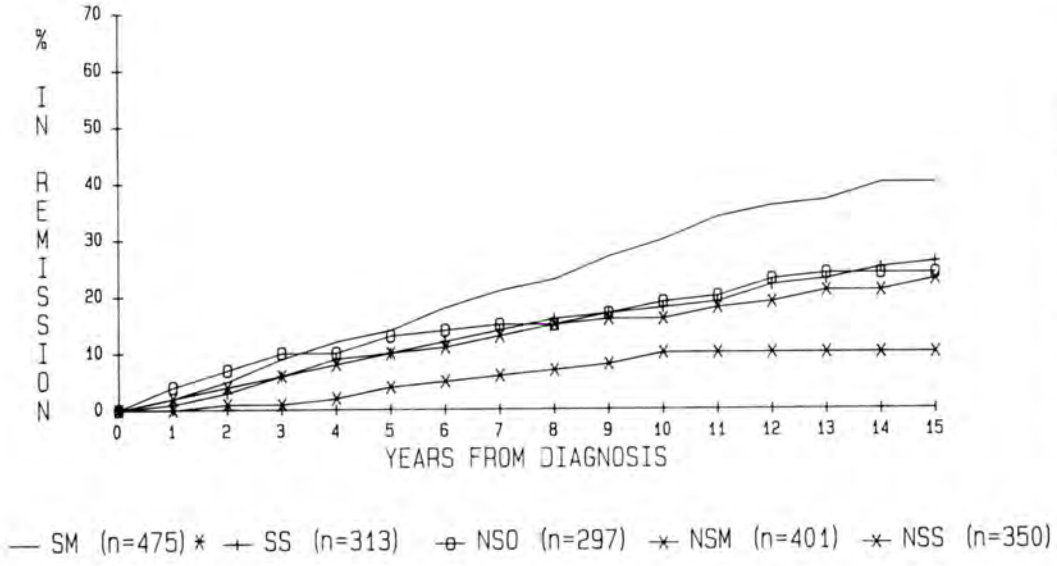

FIG. 2. Interval from diagnosis to remission in patients without thymomas in relation to treatment and severity of disease. SM: thymectomy, mild symptoms; SS: thymectomy, severe symptoms; NSO: no thymectomy, ocular symptoms; NSM: no thymectomy, mild symptoms; NSS: no thymectomy, severe symptoms. *Includes three patients with ocular disease.

TABLE 4. *Duration of Symptoms Before Thymectomy, Age, Severity of Disease, and Likelihood of Thymoma*

Duration of Symptoms	0–3 Years (%)	3–5 Years (%)	6–10 Years (%)	+10 Years (%)	Total (%)
No thymoma	591 (75)	56 (7)	55 (7)	86 (11)	788 (100)
Thymoma	153 (87)	8 (5)	5 (3)	8 (5)	174 (100)
Total	754	64	60	94	962

Age at Thymectomy	20 Years (%)	20–29 Years (%)	30–49 Years (%)	+50 Years (%)	Total (%)
No thymoma	117 (96)	215 (95)	253 (78)	203 (70)	788
Thymoma	5 (4)	11 (5)	73 (22)	85 (30)	174
Total	122 (100)	226 (100)	326 (100)	288 (100)	962
Severe Symptoms					
No thymoma	72 (96)	85 (91)	92 (64)	64 (58)	313
Thymoma	3 (4)	8 (9)	51 (36)	46 (42)	108
Total	75 (100)	93 (100)	153 (100)	110 (100)	421

were older at diagnosis, with severe forms of the disease, and those with thymoma and without thymectomy had a shorter survival. The pattern of mortality in relation to presence of thymoma and surgical treatment is shown in Figure 5. Mortality after thymectomy was significantly influenced by four independent factors (Table 7). Those patients operated on *via* a transthoracic approach, those with more severe disease, with thymomas, and older at time of diagnosis had a higher mortality.

Evaluation of the development of extrathymic neoplasms revealed 131 patients in whom the first extrathymic neoplasms were diagnosed after the onset of myasthenia gravis, and 25 patients in whom neoplasms occurred after thymectomy. Of these, 89 occurred in patients who had not undergone thymectomy and 42 occurred among patients who were operated on (Table 2). Multivariate analysis showed that in addition to the age of the patient, there were three other significant and independent factors influencing the appearance of extrathymic tumors after the diagnosis of myasthenia gravis. Earlier appearance was noted in patients with thymoma, in those who did not have thymectomy, and those who had not reached remission (Table 8).

Comparison between the postoperative courses of patients who had transcervical and transthoracic thymectomy was made after stratification by the time in which the patients had thymectomy. The majority of operations in recent years were performed by the transcervical approach. Mortality was very low in patients without thymoma, and no postoperative deaths occurred after 1973. Patients who were operated on after 1973 also had a lower postoperative morbidity in that fewer patients required tracheostomy, prolonged intubation or ventilation, or extended hospital stay (Table 9). Approximately three of four patients without thymoma who had thymectomy required hospitalization for no longer than 5 days. Within the group of patients operated on after 1973, those who had transcervical thymectomy had a significantly higher proportion of short hospitalizations and fewer tracheostomies.

Discussion

The current study clearly demonstrates that thymectomy significantly influences the clinical course in patients with myasthenia gravis. Compared with nonsurgical treatment, thymectomy is followed by an earlier onset of remissions, lower mortality, and a delay in the appearance of extrathymic neoplasms. The multivariate analysis demonstrates that the presence of a thymoma, the severity of disease, and the age of the patient are factors that significantly influence the clinical course of the disease regardless of treatment and represent independent prognostic indicators. No meaningful evaluation of treatment modalities in myasthenia gravis is possible without taking into consideration the effect of these factors. This study also confirms that thymectomy has an advantage over nonsurgical treatments[14] and that the effects of thymectomy are delayed.[2,3]

The findings indicate that even patients treated by thymectomy show an increasing percentage of remissions with increasing time intervals after diagnosis. This observation confirms previous reports[15] of delayed remissions among patients with generalized disease who

TABLE 5. *Factors Influencing Remission After Thymectomy**

	Univariate p	Stepwise p	Coefficient/SE
Severity of disease	0.0001	0.0023	2.9933
Thymoma	0.0001	0.0047	2.6193
Duration of disease	0.0846	0.0211	2.2593
Surgical approach	0.0001	0.0589	1.8396

* Number of patients = 962; number of patients in remission = 198.

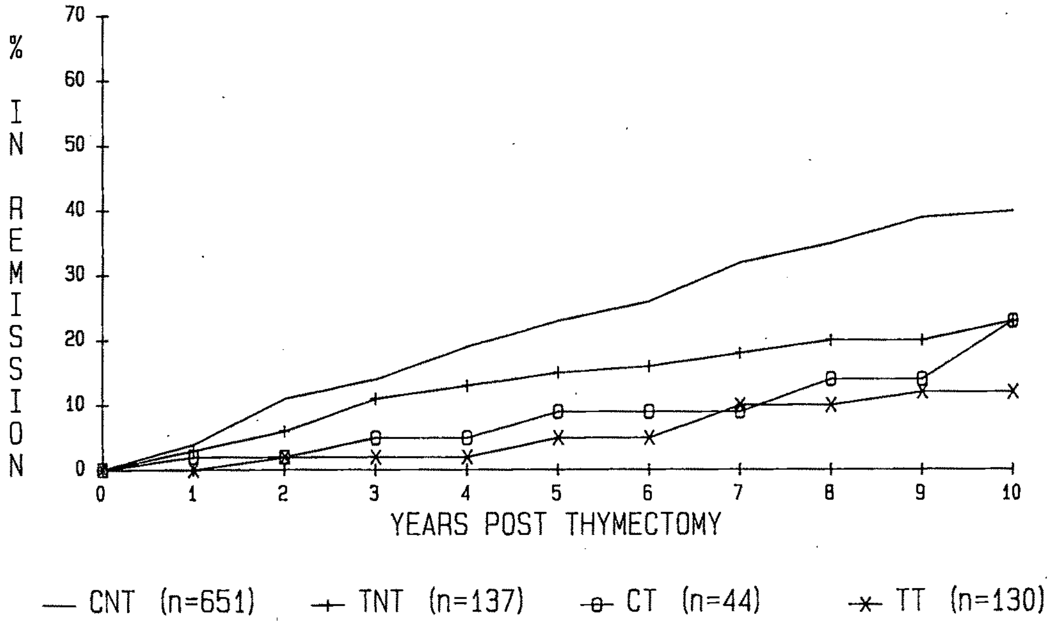

FIG. 3. Interval from thymectomy to remission in relation to thymomas and surgical approach. CNT: cervical approach, no thymoma; TNT: transthoracic approach, no thymoma; CT: cervical approach, thymoma; TT: transthoracic approach, thymoma.

were treated without surgery and does not support the previously held notion that spontaneous, or rather, nonsurgical remissions are limited to patients with ocular disease. It is obvious, therefore, that the pattern of delayed remissions, which had been demonstrated repeatedly in patients after thymectomy,[2,3,5,15] is evident in all subgroups. Results shown in Figure 2 seem to be similar to those of Oosterhuis[15] except for the ocular group, and his results suggest that overall the natural course of the disease is influenced by the same factors in both the Dutch series and ours. The difference noted in the ocular group between the two series may be associated with the less strict criteria used by Oosterhuis, who included patients with sporadic diplopia and ptosis when fatigued at the end of the day in the remission group.

From the observed differences in remission and/or in mortality, among patients treated with and without thymectomy, it appears that the role of thymectomy is to avert progression of the disease, decrease mortality, and accelerate the onset of remission.

The difficulty in evaluating the results of treatment

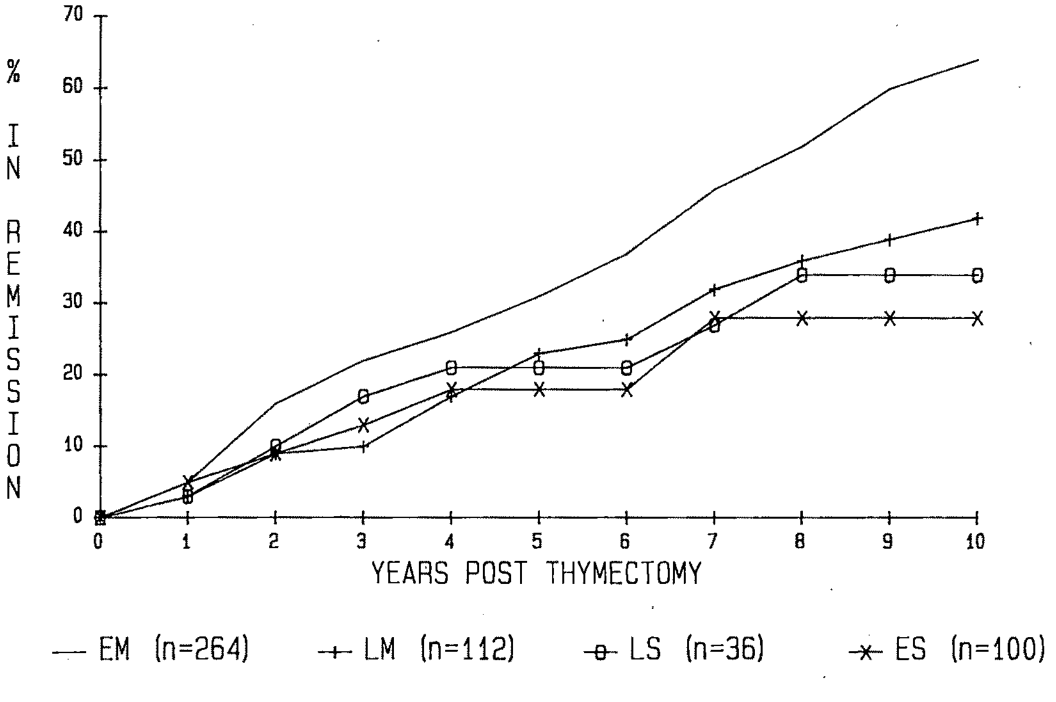

FIG. 4. Interval from thymectomy to remission in patients without thymoma operated on by AEP. EM: short duration and mild symptoms; LM: long duration and mild symptoms; LS: long duration and severe symptoms; TS: short duration and severe symptoms.

modalities without considering potential confounders is further complicated by the facts that thymomas occur more frequently in association with severe disease, are frequently undetected on routine roentgenograms, and may have been unrecognized in previous years when thymectomy was performed only in young patients in whom nonsurgical treatment had failed. The data in Table 4 indicate that approximately 10% of patients who had thymectomy more than 3 years after onset of myasthenia had thymomas and that these were more frequent than had been previously noted among older patients with severe symptoms. Although the adverse clinical course of patients with thymoma has been known for many years,[1,15] the independent impact of the severity of disease on the clinical course has not been previously appreciated.

The findings of our study (Fig. 2) lend support to Schumm's suggestion[16] that thymectomy is indicated in ocular cases. Since thymectomy stops progression of the disease, early intervention before the symptoms become generalized may be advisable. Thymectomy, particularly when performed *via* the transcervical approach, has minimal morbidity and is devoid of the risk of side effects from immunosuppressive drugs. The inability to determine the clinical course of the disease at the time of onset of symptoms[17] and the inability to exclude the presence of thymoma are additional indications for early intervention.

The current study also casts doubt on the validity of the earlier concepts that the sex of the patient influences therapeutic results and that patients over the age of 40 do not do well after thymectomy, as neither sex nor age entered the stepwise analysis when the interval to remission was analyzed (Tables 3 and 5). This confirms the results of our previous report that evaluated thymectomy in patients over the age of 40.[18]

TABLE 6. *Factors Influencing Mortality After Diagnosis in All Patients**

Variable	Univariate p	Stepwise p	Coefficient/SE
Class at diagnosis	0.0000	0.0000	8.6581
Age at onset	0.0000	0.0000	9.9893
Thymoma	0.0000	0.0000	8.4123
Thymectomy	0.0000	0.0000	5.2179

* Number of patients = 2062; number of patients who died = 391.

In recent years thymectomy has become recognized as an established therapeutic procedure,[14,19] and arguments as to whether thymectomy should be performed in myasthenia gravis have taken second place to the question of which is the appropriate surgical approach to the thymus. The focus of the controversy has been the feasibility of complete removal of the thymus *via* the transcervical approach rather than the advantage offered by the surgical approach in terms of superior long-term clinical results. Proponents of the transthoracic approaches and advocates of radical thymectomy, which includes removal of mediastinal fat through a combined transcervical and transthoracic approach, have failed to prove a relevant clinical advantage of these procedures over the transcervical approach.[10] Therefore, the argument that a more complete thymectomy can be achieved with the radical approach is a moot point if

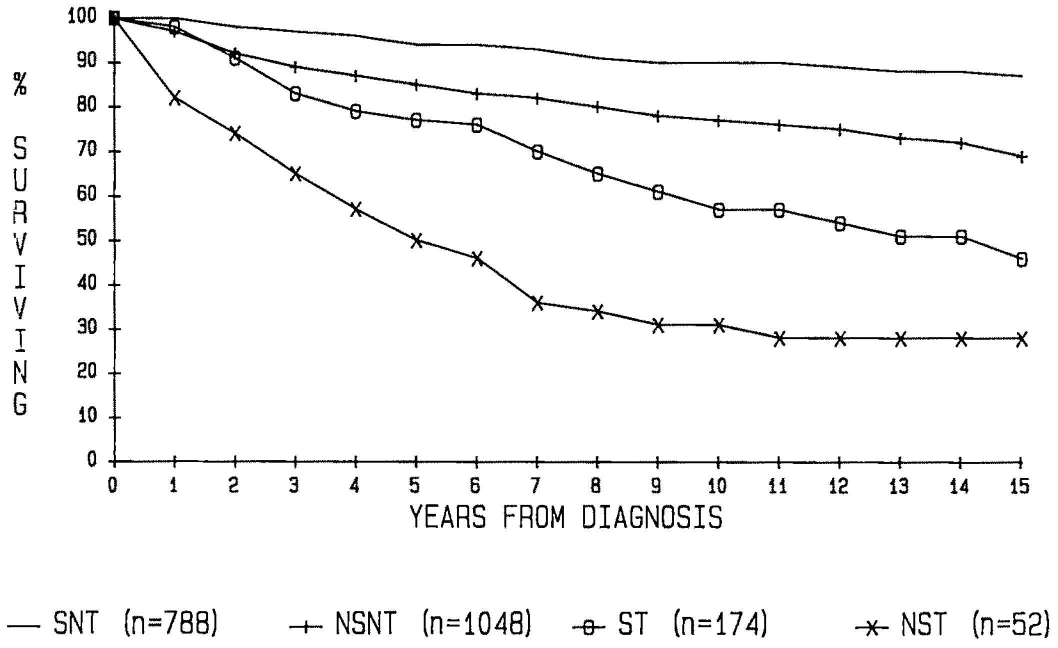

FIG. 5. Interval from diagnosis to death. SNT: thymectomy, no thymoma; NSNT: no thymectomy, no thymoma; ST: thymectomy, thymoma; NST: no thymectomy, thymoma.

TABLE 7. *Factors Influencing Mortality After Thymectomy**

Variable	Univariate p	Stepwise p	Coefficient/SE
Age at onset	0.0000	0.0001	3.9520
Severity of disease	0.0000	0.0011	3.8421
Thymoma	0.0000	0.0006	3.4280
Surgical approach	0.0000	0.0029	2.9265

* Number of patients = 962; number of patients who died = 139.

superior clinical results cannot be demonstrated after the use of this technique.

The current study, which addresses the question of whether surgical approach influences the clinical results, does not provide any evidence for advocating a transthoracic removal of the thymus. Indeed, even after considering the effect of independent confounders, a slight advantage of the transcervical approach persisted in terms of long-term results (Table 5). The highly significant advantage of the transcervical approach noted in the univariate analysis was not as significant in the stepwise analysis, indicating that most of it could be explained by the fact that the transcervical technique was used more frequently in patients without thymomas, in those with milder disease, and in those having a shorter duration of symptoms. It is clear that severity of disease and timing of operation affect the results more significantly than the approach, and that the best results were obtained in the group of patients who were treated with early intervention, before clinical progression of the disease. Two additional reports, from surgeons having a large experience with the transcervical approach, substantiate the advantage for early intervention.[8,20] Patients operated on by AEP had earlier onset of remission but this may also reflect a more complete follow-up as similar advantages were noted in patients operated on at our institution after 1973. In earlier years, asymptomatic patients were discharged from follow-up studies. Further analysis would be necessary to determine the cause for this advantage in these patients.

TABLE 8. *Factors Influencing Development of Extrathymic Neoplasms After Diagnosis**

Variable	Univariate p	Stepwise p	Coefficient/SE
Age of patient	0.0000	0.0000	5.5203
Thymoma	0.0109	0.0000	4.7650
Thymectomy†	0.0000	0.0000	−4.4702
Remission	0.0001	0.0039	−2.5917

* Number of patients = 2062; number of neoplasms = 131.

† Neoplasms occurring in operated patients before thymectomy listed as occurring in patients without thymectomy.

The experimental findings indicating that the protective effect of thymectomy against neoplasms is superior in mice operated on by a technique that results in retention of thymic remnants, compared with a technique that is associated with a complete removal of the thymus,[21] add additional doubts as to the validity of advocating a radical approach to thymectomy. The thymus, which is considered to have an endocrine function, is embryologically derived from the same brachial pouches as the parathyroid, whereas abnormalities of thyroid function are frequent in myasthenic patients.[11] The endocrine mechanism in myasthenia was pointed out by Simpson.[22] If we extrapolate from the experience obtained with thyroid and parathyroid surgery, complete excision of the endocrine gland for hyperthyroidism or primary hyperparathyroidism is rarely indicated and sufficient control is obtained in the majority (approximately 90%) of cases even with a subtotal removal. It is therefore difficult to justify the persistent calls for radical thymectomy since there is neither clinical evidence of, nor scientific basis for, advocating such an approach. Most surgeons who have had experience with the transcervical approach[7–9] prefer it over the transsternal approach, and they agree that the long-term results are comparable to those obtained with the transthoracic approach. In addition, the immediate postoperative course is smoother as a result of the minimal operative trauma. Some of the proponents of the transcervical approach do not recommend it in patients with thymomas,[7] but those who have become familiar with the technique and have used it extensively[5,8,23] report removal of small thymomas, when technically feasible, through the neck incision. The results in Figure 3 indicate that there is no clinical disadvantage when thymomas are removed by the transcervical approach and therefore the alleged disadvantage of the transcervical approach in terms of exposure does not appear to have any clinical relevance.

Residual thymus, or regeneration of the gland after thymectomy, has been implicated in the failure of the procedure to result in remission in all cases. Because of the delayed clinical response after thymectomy, which is influenced by factors unrelated to treatment and surgical technique, it is difficult to identify patients who might benefit from re-exploration to remove residual thymic tissue. Indications for re-exploration in the 10–15% of patients who fail to respond to thymectomy should be based on clinical course or computerized tomographic (CT scan) findings. Re-exploration for residual or ectopic thymus may be indicated, regardless of the original approach, if a patient shows signs of progressive deterioration of symptoms after a prolonged and sustained improvement. Additional thymic tissue has been found in patients operated on originally by both transcervical and transsternal approaches.[24–26] In our series one of the six patients who had reached remission after thymectomy had a relapse of symptoms 5 years later,

TABLE 9. *Postoperative Course*

	Before 1973				1973–1986			
	Thoracic		Cervical		Thoracic		Cervical	
Thymoma	−	+	−	+	−	+	−	+
All patients	108	88	103	4	28	44	548	40
Mortality								
Number of patients	33	7	1	0	0	0	0	0
Percentage	3%	8%	0.9%	0	0	0	0	0
With tracheostomy								
Number of patients	73	51	72	3	3	3	24	2
Percentage	68%	58%	69%	75%	11%	7%	4%	5%
Length of stay*								
3–5 days								
Number of patients	1	0	7	0	4	6	325	21
Percentage	4%	0%	13%	0%	40%	16%	78%	64%
6–9 days								
Number of patients	2	1	5	1	2	8	36	5
Percentage	8%	5%	9%	33%	20%	42%	9%	15%
10+ days								
Number of patients	21	17	42	2	4	10	58	7
Percentage	88%	85%	78%	67%	40%	42%	14%	21%
TOTAL	24	18	54	3	10	24	419	33
Delay in Extubation over 30 Minutes†								
Number of patients with delay					0	1	11	0
Percentage					0%	25%	11%	0%
Total					2	4	93	6
Percentage					100%	100%	100%	100%

* Data available in 585 patients.

† Data available in 105 consecutive patients operated on in 1983–1986.

had re-exploration, and residual thymus was removed. Relapse of symptoms after remission seems to be rare both in our experience and in other reports.[27] Whether the removal of residual tissue will benefit the patient is not clear as long-term follow-up information in these patients is not yet available. Blalock's original technique, as pointed out in the report of Mulder et al.,[27] was not a complete thymectomy, yet the patient derived a definite benefit.

The current study did not address the issue of specific mortality from myasthenia gravis because the cause of death was not always readily available from the records. It would be of interest to address this issue in future analyses, taking into consideration the possibility of increased mortality from associated extrathymic neoplasms in patients who had not had thymectomy.

Previous studies have suggested that there is an increased incidence of extrathymic neoplasia among myasthenic patients and that thymectomy is not followed by this increased incidence of extrathymic tumors.[4,28,29] The current study confirms that development of extrathymic neoplasms after the diagnosis of myasthenia gravis is significantly less frequent among those patients who had had thymectomy.

Thymectomy, particularly when performed by the transcervical approach, is evidently a safe procedure associated with minimal morbidity. Complete information on the immediate postoperative course was not available in all our patients. The available results (Table 9) indicate that in recent years (1983–1986), need for postoperative ventilation and frequency of tracheostomy have been decreasing.

Of 92 consecutive patients who had thymectomy from 1983 to 1985 and who were monitored in the postoperative period, only eight (8.7%) who had transcervical thymectomy required postoperative mechanical ventilation for more than 3 hours as we previously reported.[30] Other centers report that patients who have transsternal thymectomy require prolonged mechanical respiratory assistance far more frequently.[31–33] Routine tracheostomy used to be commonplace in previous years when the transsternal approach was used, and this accounts for the high proportion of tracheostomies shown in Figure 9 for the period preceding 1973. Even in more recent series of transsternal thymectomies, 30% of patients required mechanical ventilation for more than 3 days and 7% required tracheostomy.[33] In our series only 26 of the 588 patients (4%) who had transcervical thymectomy after 1973 required tracheostomy, whereas intubation beyond 0.5 hour after completion of surgery was required in only 10% (Table 9). Early extubation was also noted in other centers using the transcervical approach.[34] Although thymectomy through the neck was described as a procedure taking 15–20 minutes,[35] in our experience the operating time is rarely less than 20 minutes and is more frequently 60–90 minutes. The difference may be due to the fact that thymic hyperplasia is encountered in most myasthenic patients and this necessitates additional blunt dissection to achieve good visualization of the lower attachments of the thymic lobes. Longer operative time is also necessary when parasternal mediastinoscopy[36] is required for removal of small thymomas.

In today's budget-conscious environment it is difficult to justify the added cost of technical procedures that have disadvantages in terms of immediate morbidity and no advantage in terms of long-term clinical results. Considering both long- and short-term advantages as well as efficient use of health resources, it would seem that early surgical intervention, *via* the transcervical approach when technically feasible, represents the treatment of choice for patients with myasthenia gravis.

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A Dose-responsive Model of Smoke Inhalation Injury

Severity-related Alteration in Cardiopulmonary Function

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The dose responsiveness of selected physiologic indices was studied in a sheep model of smoke inhalation injury. In this model, graded severity of injury was achieved by changing the contact time with smoke (defined by "unit"), whereas other variables were kept constant. Blood gas and cardiopulmonary indices were measured in 70 sheep, including 12 controls, either 24 or 72 hours after exposure to 3, 6, 9, 12, 15, or 18 units of smoke. A 12-unit dose of smoke was fatal within 72 hours and an 18-unit dose was fatal within 24 hours. The best correlation between smoke dose and response was observed in arterial oxygen tension 24 hours after exposure. At 24 hours, most of the cardiopulmonary indices showed significant change only after a 12-unit exposure. Although the exact shape of the dose-response curve could not be defined, sigmoid or curved linear shape was suggested, reflecting the progressive deterioration.

SMOKE INHALATION INJURY is one of the primary determinants of survival after major burns.[1] The significance of pulmonary injury due to smoke inhalation in burn patients was not widely realized until the 1970s, although antecedent work by Phillips had indicated the likelihood that such injury was of consequence.[2-4] In recent years early diagnosis of smoke inhalation and evaluation of its severity have achieved wide clinical interest, but even now the pathophysiologic mechanisms of the injury are not clear. Although several animal models have been developed to study such mechanisms, they have either been small animal models[5-8] or failed to permit control of severity.[9-12] We have developed a sheep model of smoke inhalation injury that is reproducible and dose-responsive.

Sheep are large enough to allow detailed physiologic monitoring and frequent blood sampling.[13-14] A technique for lung lymph cannulation has also been established for sheep.[15] In this model, dose responsiveness was assessed by changing the duration of smoke exposure to the lung while keeping other factors that influence severity unchanged. The severity of smoke inhalation injury is related to smoke temperature, chemical and physical composition of the smoke (gas, vapor, and particle), contact time (time exposed to smoke), and contact area (depth of breath). In the current system, the smoke was equilibrated at ambient temperature to exclude all possibility of thermal injury to the airway. The animals were exposed to a volume of smoke proportional to their body weight. The severity of injury in a spontaneously breathing animal is also influenced by hyperventilation in response to the carbon monoxide content of the smoke.[16] Spontaneously breathing animals with elongated nasal passages, with epiglottic closure, or with early bronchospasm may show further variability in severity of injury.[12] In this work, smoke exposure was done under general anesthesia using endotracheal intubation to avoid changes in the depth of breath that affect contact area. With respect to smoke

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In conducting the research described in this report, the investigators adhered to the Animal Welfare Act and other Federal statutes and regulations relating to animals and experiments involving animals and with the *Guide for the Care and Use of Laboratory Animals,* National Institutes of Health Publication 80-23.

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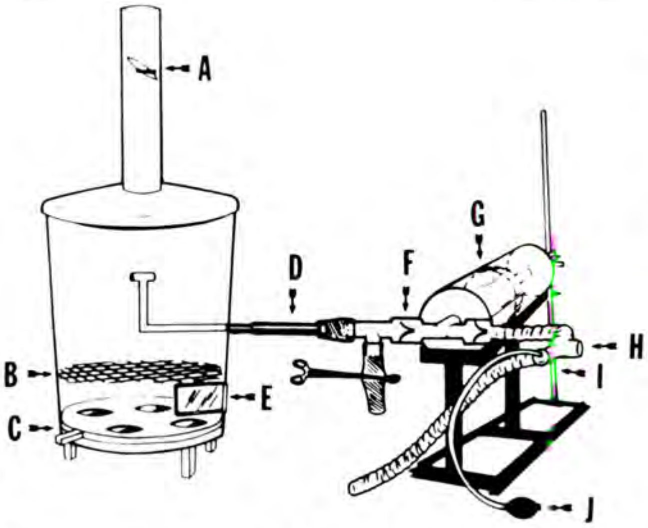

FIG. 1. Schematic presentation of smoke generator and smoke delivery system. Disposable underpads are burned in the smoke generator. Smoke is introduced through the copper pipe (D) to the volume-adjustable metal syringe (G). Either smoke or air is introduced into the pump by clamping the other rubber connection. Animals are intubated and connected to the outlet (H). Animals are insufflated with smoke when the exhalation valve (I) is closed manually by pressing the rubber bulb (J). (A) Damper; (B) Mesh; (C) Adjustable air inlet; (E) Window; (F) One-way valve.

composition, fluctuation of combustion was minimized by the relatively large size of the combustion chamber (32 gallons, 122 liters).

After smoke exposure, the sheep were extubated and allowed to breathe spontaneously to assess the natural history of smoke inhalation injury. Twenty-four or 72 hours after smoke inhalation, the sheep were reanesthetized, intubated, and catheterized for the measurement of pulmonary arterial and systemic arterial pressures. After a 2-hour stabilization period, cardiopulmonary indices were measured under anesthesia, using mechanical ventilation, a state that corresponds to the situation in patients in an intensive care unit setting.

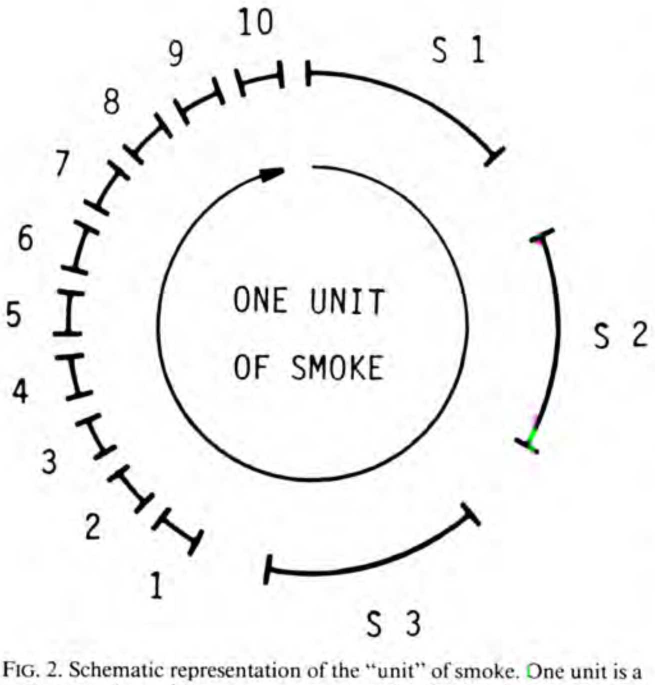

FIG. 2. Schematic representation of the "unit" of smoke. One unit is a cycle comprised of three exposures to smoke (S1–S3) followed by ten short ventilations with air. See text for details.

This report describes the dose dependence of alterations in cardiopulmonary function after smoke inhalation.

Materials and Methods

Animals

One- to two-year-old neutered male, commercially available, random source sheep weighing 30.8 ± 4.3 kg (mean ± SD) were used in this study. The animals were housed in covered outdoor runs, treated for parasites, and fed commercial chow and water *ad libitum*. Baseline complete blood counts, total proteins, and blood chemistries were done 3 weeks before experimental use. The animals were fasted for 24 hours before smoke exposure and experimental use. Twelve sheep were used as controls and 58 were exposed to smoke; 41 sheep were studied 24 hours after smoke exposure and 17 sheep were studied 72 hours after exposure. Immediately after smoke inhalation, the sheep were housed in climate-controlled facilities at 74–76 F (24–25 C) and a relative humidity of 40–50%.

Smoke Generation and Exposure

Smoke was produced by burning 10 disposable underpads (45 × 52.5 cm, 40 g each, Hosposable, Inc., Bound Brook, NJ) made of polyethylene, wood pulp, and nonwoven cellulose fabric. The smoke generator was a 32-gallon metal container equipped with an air inlet, a dampered chimney, a window, and smoke outlet (Fig. 1). The smoke passed through a copper pipe (30 × 1.6 cm) into a volume-adjustable metal syringe, which permitted insufflation of either smoke or air. The smoke reached ambient temperature during passage through the pipe and delivery system and contained 10–14% oxygen, 3–8% carbon dioxide, 0.7–2.2% carbon monoxide, and other combustion products (methane, ethylene, propylene, and acetaldehyde), but no cyanide.

The experimental sheep were individually exposed to 3, 6, 9, 12, 15, or 18 units of smoke. One unit of smoke consisted of three successive exposures to smoke with a tidal volume of 30 mL/kg and breath hold of 5 seconds followed by 10 successive ventilations with room air (Fig. 2). The time required per unit was about 50 seconds. Before smoke insufflation, the sheep were intubated, anesthetized with methohexital sodium (9 mg/kg, Brevital® Sodium, Eli Lilly and Company, Indianapolis, IN) and paralyzed with succinylcholine chloride (0.7 mg/kg). The sheep were extubated after smoke inhalation. Of the 41 sheep studied 24 hours after smoke exposure, six sheep were exposed to 3 units of smoke, eight sheep to 6 units, nine sheep to 9 units, seven sheep to 12 units, seven sheep to 15 units, and four sheep to 18 units. For the 72-hour studies, seven, six, and four sheep were exposed to 6, 9, and 12 units of smoke, respectively.

Monitoring

Sheep were studied 24 or 72 hours after smoke inhalation. On the day of measurement, arterial and central venous lines, a Swan-Ganz catheter (7F, American Edwards Laboratories, Irvine, CA), a lung water catheter (American Edwards Laboratories), and an esophageal balloon were inserted after general anesthesia and intubation. Anesthesia was induced with methohexital sodium (9 mg/kg) and maintained with alpha-chloralose (0.05 g/kg, Calbiochem®, La Jolla, CA) and the sheep were paralyzed with pancuronium bromide (0.03–0.04 mg/kg, Pavulon®, Organon Pharmaceuticals, West Orange, NJ). After the placement of catheters, the animals were positioned prone and artificially ventilated. A volume-limited ventilator (Bear 2™, Bear Medical Systems, Inc., Riverside, CA) with a tidal volume of 15 mL/kg was used at a respiratory rate of 12 per minute. Sigh ventilation with a tidal volume of 21 mL/kg was applied every 3 minutes to prevent atelectasis. Lactated Ringer's solution was continuously infused at a rate of 1 mL/kg per hour.

Central venous pressure and pulmonary artery pressure (PAP) were monitored with Statham P23Db transducers (Statham Instruments, Oxnard, CA) and systemic arterial pressure was monitored with a Hewlett-Packard 1290A quartz transducer (Hewlett-Packard Company, Waltham, MA). These pressures were recorded on a Hewlett-Packard four-channel recorder (Model 7754A). Respiratory indices were monitored with a pneumotachograph (Model 17212, Gould, Inc., The Netherlands) for flow rate and tidal volume and a differential transducer (MP-451, Validine Engineering Corporation, Northridge, CA) for transpulmonary pressure, with the pulmonary variables recorded on another Hewlett-Packard four-channel recorder (Model 7754A). Cardiac output was measured in triplicate by thermodilution technique (cardiac output computer, Model 9520A, American Edwards Laboratories) and lung water was measured by thermal-dye double indicator-dilution method (lung water computer, Model 9310, American Edwards Company). Blood gas analysis was performed using an IL 1303 pH/blood gas analyzer and an IL 282 CO-Oximeter (Instrumentation Laboratories, Inc., Lexington, MA). Cardiopulmonary indices and blood gas levels were measured every 30 minutes, and the values measured after 2 hours of stabilization were taken as representative values.

Necropsies were performed on all sheep dying spontaneously or sacrificed at the end of the experiments. A complete set of tissues was fixed in 10% neutral buffered formalin and processed by standard methods. The locations of the tissue sample collection sites were midtrachea, tracheal bifurcation, right and left proximal and distal bronchi, apical and diaphragmatic lobes, and any other morphologically significant foci.

Data are displayed as mean ± SE. Regression analysis by least-square technique was used to examine the linear relationship between physiologic variables and the number of units of smoke. Linear regression analyses included the control sheep unless otherwise indicated. Survival rate was analyzed by stepwise logistic regression. Multiple comparisons were done by one-way analysis of variance (Tukey studentized range method and the Student-Newman-Keuls multiple range test). Differences were considered significant at $p < 0.05$.[17]

Results

Sheep resumed spontaneous breathing soon after smoke exposure, and breathing was supported by an ambu-bag until they were extubated. The sheep usually started walking within 10 minutes after smoke exposure. Sheep exposed to smoke showed symptoms such as coughing, wheezing, and frothing beginning 4–6 hours after smoke exposure. All sheep in which physiologic measurements were made could breathe spontaneously and stand unassisted, although sheep exposed to 12 units or more showed distinct respiratory distress.

Sloughing of the airway epithelium occurred consistently in sheep exposed to smoke (Fig. 3). This pseudomembrane formation was typically seen in major airways and became progressively thicker in sheep exposed to higher doses of smoke. At autopsy, almost complete occlusion of the trachea was seen in sheep that died spontaneously 12 or more hours after exposure. Histologic changes of the airways included disruption, swelling, and loss of cilia (Fig. 4A). Increased numbers of inflammatory cells were common in the laminae propriae, respiratory mucosae, and airway lumina. Surface accumulation of mucocellular debris, often with obstruction, was associated with parenchymal congestion, edema, and atelectasis (Fig. 4B). These parenchymal changes were most prominent in the dependent areas of the lung.

Mortality at 24 and 72 hours is shown in Figure 5. Six units or less of smoke was not fatal by 72 hours, but 12-unit doses were fatal by 72 hours. Therefore, 15- or

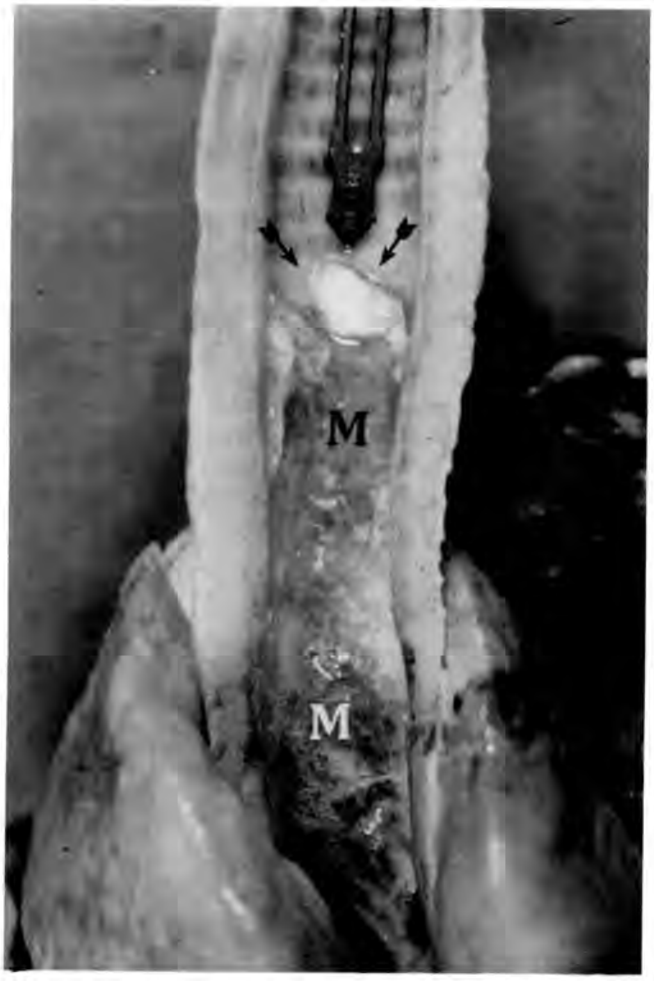

FIG. 3. Trachea of a sheep 24 hours after exposure to 9 units of smoke. This photo illustrates the formation of a pseudomembrane (M) in the trachea and bronchi. The membrane is separating from the underlying epithelium (arrows) and partially occludes the trachea and lower respiratory tract.

18-unit smoke exposures were not studied for survival or physiologic response at 72 hours. Eighteen-unit doses were fatal by 24 hours; one of the four sheep receiving an 18-unit dose died within 1 hour after exposure and three others died between 5 and 15 hours after exposure. Mortality at 24 hours was well predicted by the logistic model (mortality = exp(y)/(1 + exp(y)), where $y = 0.535x - 7.865$ and x = number of smoke dose units). According to this equation, the best logistic regression estimation of LD_{50} at 24 hours was 14.7 units of smoke. Data were insufficient for statistical analysis at 72 hours.

Carboxyhemoglobin levels immediately after smoke exposure are shown in Figure 6. Even 3 units of smoke raised the carboxyhemoglobin level over 40%. Eighteen units of smoke elevated the mean blood carboxyhemoglobin level to 85.4 ± 2.6%.

The arterial oxygen tension (PaO_2) of each group is shown in Figure 7. Control sheep had an average PaO_2 of 88.9 ± 1.2 torr (N = 12, electrode at 37 C). Sheep exposed to 9 units or more had significantly lower PaO_2 than the controls at both 24 and 72 hours after smoke exposure. At 24 hours after smoke inhalation, PaO_2 (y = torr) was negatively related to the number of units of smoke exposure (x = units): $y = 90.0 - 3.24x$ ($r^2 = 0.646$, N = 44, $p < 0.01$). The data were insufficient for statistical analysis at 72 hours.

At 24 hours, none of the sheep exposed to 9 units or less of smoke showed significant depression of plasma

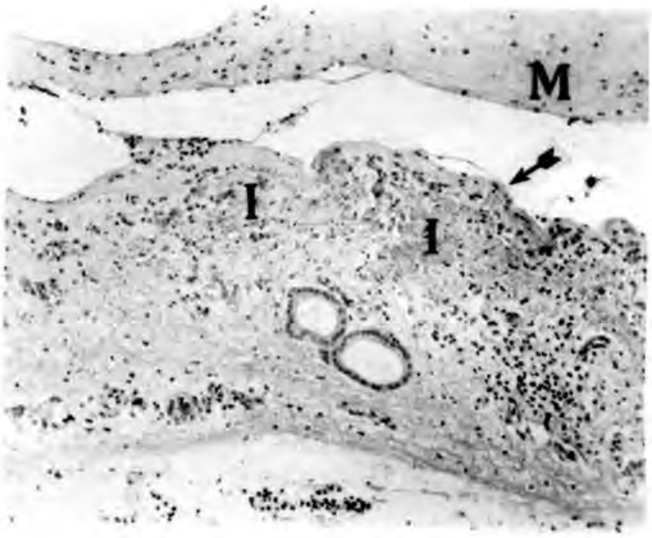

FIG. 4A. Histologic changes at 24 hours after exposure to 9 units of smoke. Note the sloughing of necrotic tracheal epithelium (arrow), the inflammatory cell infiltration (I), and the presence of a thick pseudomembrane (M). (Hematoxylin and eosin, original magnification ×370.)

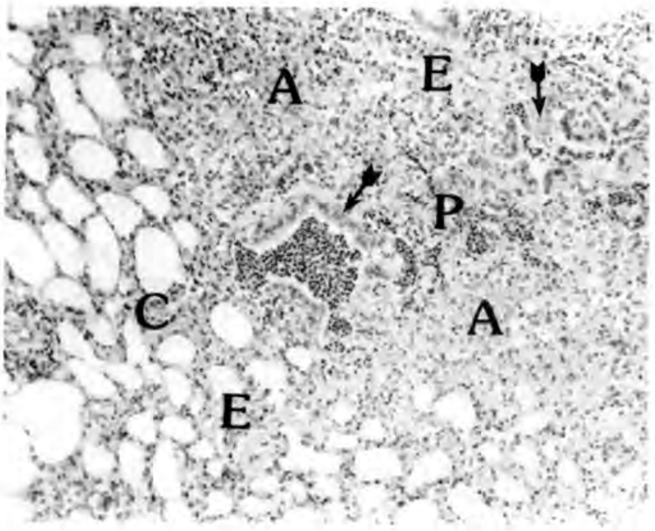

FIG. 4B. Parenchymal changes are shown. Occlusion of bronchioles (arrows) by inflammatory cells and necrotic debris is noted with concomitant atelectasis (A), congestion (C), edema (E), and pneumonia (P). (Hematoxylin and eosin, original magnification ×370.)

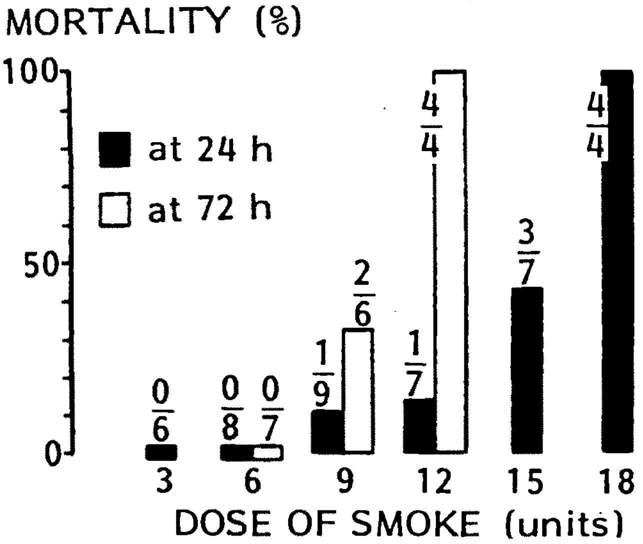

FIG. 5. Mortality at 24 hours (solid bars) and 72 hours (open bars) after smoke exposure. Mortality is shown as percentage. Fractions on the bars are actual number of dead sheep (numerator)/number of sheep studied (denominator). Mortality at 72 hours for 15 or 18 units of smoke exposure was not studied because 12 units of smoke was already fatal by 72 hours.

pH (Table 1). Some of the sheep exposed to 9 units or more had elevated plasma $PaCO_2$ at 24 hours, but this was not a consistent finding (Table 1). At 72 hours, surviving sheep exhibited no acidosis, but one had hypercapnea ($PaCO_2 = 42$ torr).

Mean blood pressure (mBP, y = torr) also showed dose responsiveness (Fig. 8) between 3 and 15 units of smoke (x = smoke units) at 24 hours: $y = 136.0 - 3.55x$ ($r^2 = 0.439$, $N = 32$, $p < 0.01$). Sheep exposed to 3 units of smoke showed highly elevated blood pressure and those exposed to 12 units or more had significantly lower blood pressure than others. The data at 72 hours were not sufficient for such analysis. Sheep exposed to 12 units or more also showed significantly increased PAP at 24 hours (Table 1).

Cardiac index (CI) was higher in the 3-unit and 6-unit groups than in controls at 24 hours, but the difference was not statistically significant (Table 1). At 9- and 12-unit doses, CI decreased progressively, but the CI of the 15-unit group did not differ significantly from control. A significant difference of CI was seen only between the 6-unit and 12-unit dose groups at 24 hours. At 24 hours, the left ventricular stroke work index (LVSWI) of the 12-unit group was significantly lower than the preinjury level. No significant differences in total peripheral resistance index (TPRI) were noted in any group.

Pulmonary resistance (PR) was significantly elevated at 24 hours in sheep exposed to 9 units or more and at 72 hours in sheep exposed to 9 units of smoke (Fig. 9). Lung static compliance changes were the reciprocal of

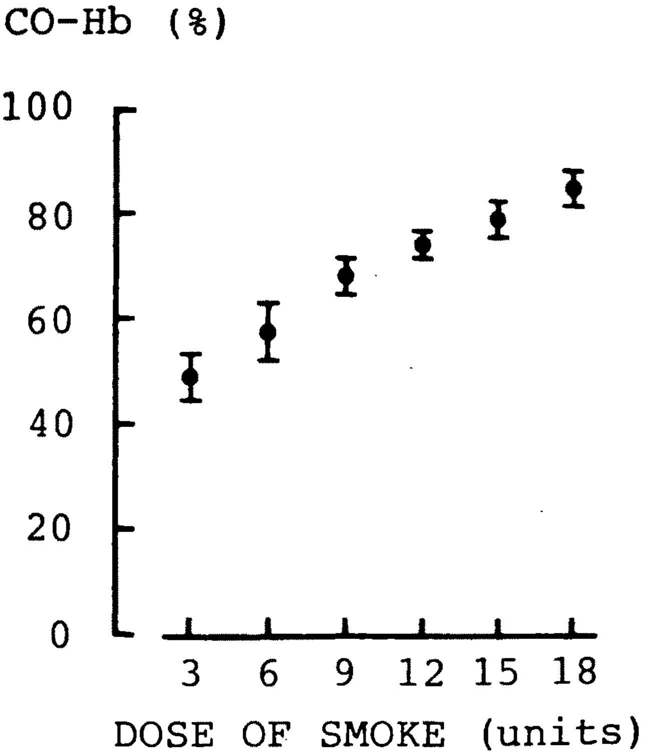

FIG. 6. Peak levels of carboxyhemoglobin (CO-Hb). Blood samples were taken immediately after smoke exposure from the external jugular vein.

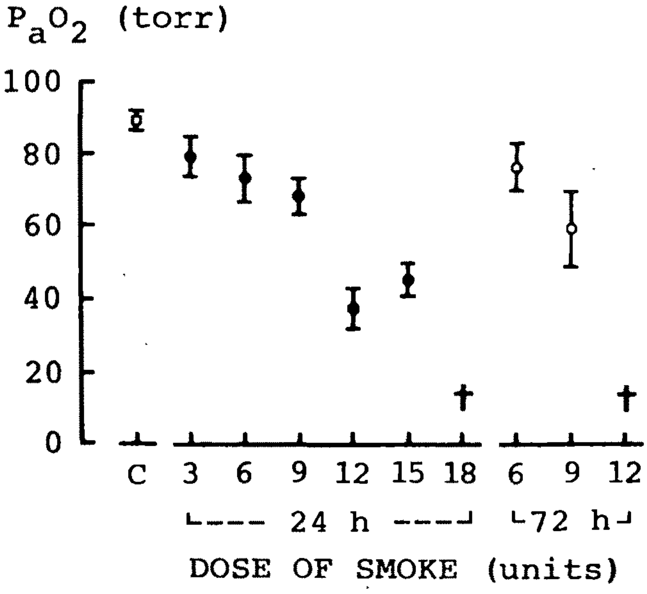

FIG. 7. Arterial oxygen tension (PaO_2) of the control (C) and smoke-exposed groups. Crosses (+) show that all the sheep in that group had died by the time of physiologic measurement. At 24 hours after smoke inhalation, PaO_2 (y = torr) was negatively related to the number of units of smoke expsoure (x = units): $y = 90.0 - 3.24x$ ($r^2 = 0.646$, $N = 44$, $p < 0.01$). The data at 72 hours were not sufficient for statistical analysis. Note that the values shown here are direct readings from the electrode set at 37 C. The actual PaO_2 in the sheep is 7–12 torr higher after temperature correction for their body temperature (39.5–40.0 C).

TABLE 1. *Other Cardiopulmonary Indices in Each Group (Mean ± SE)*

	Control	24 Hours after Exposure						72 Hours after Exposure		
Smoke (units)	—	3	6	9	12	15	18	6	9	12
Number of sheep	12	6	8	9	7	7	4	7	6	4
Arterial pH	7.49	7.50	7.52	7.49	7.35	7.46	—	7.54	7.44	—
	0.02	0.01	0.02	0.02	0.05	0.05	—	0.01	0.03	—
$PaCO_2$ (torr)*	30.3	30.2	29.1	30.0	40.0	36.8	—	29.6	32.5	—
	1.2	0.3	0.9	1.4	3.2	1.9	—	1.5	3.6	—
mPAP (torr)	9.3	12.0	10.3	14.7	19.1	20.5	—	9.7	11.6	—
	1.1	1.7	1.4	2.1	2.1	1.4	—	1.4	0.7	—
CI (L/min/m^2)	3.4	3.7	4.2	3.7	2.9	3.2	—	3.5	3.5	—
	0.2	0.2	0.2	0.3	0.4	0.2	—	0.2	0.4	—
LVSWI	33.3	41.2	35.0	32.3	17.8	31.1	—	24.9	30.2	—
	3.4	3.3	1.8	2.5	2.7	2.9	—	2.7	4.4	—
TPRI	2627	2704	2110	2516	2519	2151	—	2835	2395	—
	145	163	98	248	375	376	—	256	260	—
EVLWV (mL/kg)	9.2	12.6	11.4	12.3	18.0	13.4	—	11.7	10.9	—
	0.5	1.1	0.5	1.3	1.5	1.8	—	0.5	1.4	—

* $PaCO_2$ values are direct readings from the electrode set at 37 C.

mPAP = mean pulmonary artery pressure; LVSWI = left ventricular stroke work index (g-m/m^2); CI = cardiac index; TPRI = total peripheral resistance index (dynes sec m^2/cm^5); EVLWV = extravascular lung water volume.

those in PR; compliance was significantly lower at 24 hours in sheep exposed to 12 units or more and at 72 hours in sheep exposed to 9 units (Fig. 10).

At 24 hours, extravascular lung water was significantly elevated in sheep exposed to 12 units compared with the controls or to those sheep exposed to 9 units of smoke or less. No significant difference was found between the 12-unit and 15-unit groups (Table 1).

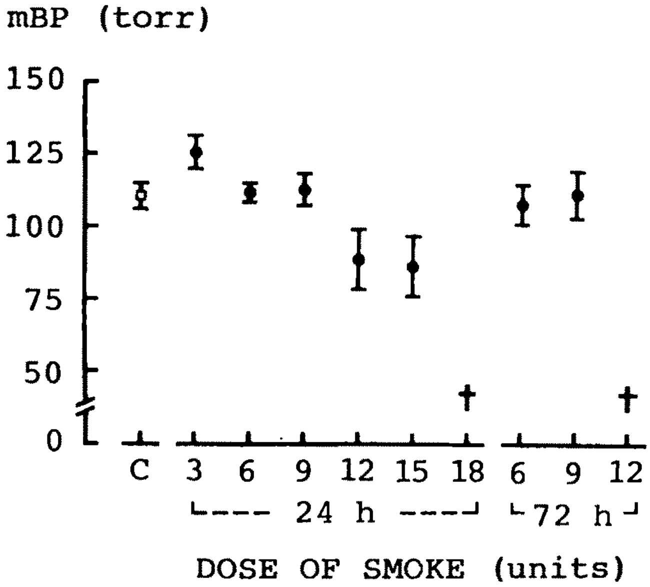

FIG. 8. Mean blood pressure (mBP) of each group. At 24 hours, mBP (y = torr) showed similar relationship to PaO_2 between 3 and 15 units of smoke (x = units): $y = 136.0 - 3.55x$ ($r^2 = 0.439$, N = 32, $p < 0.01$). The data at 72 hours were not sufficient for such analysis.

Discussion

In this model, anesthetized sheep were insufflated with smoke, using endotracheal intubation, to inflict a consistent reproducible injury to the lung. After smoke exposure, the sheep were extubated and allowed to breathe spontaneously. Twenty-four or 72 hours after smoke inhalation, the sheep were reanesthetized, intubated, and catheterized for physiologic evaluation. After a 2-hour stabilization period, cardiopulmonary indices were measured under general anesthesia and mechanical ventilation. We used alpha-chloralose as the anesthetic agent because this agent exerts only minimal effects on cardiopulmonary function.[18] We returned the sheep to the prone position as soon as the catheters were placed to avoid any adverse effects of the supine position. Prolonged supine positioning causes congestion in the lung, frothing, and cyanosis.[19] Sigh ventilation was used to prevent atelectasis, which is likely to develop in sheep, even in the prone position. In exposing the sheep to smoke, a tidal volume of 30 mL/kg was used. This tidal volume did not present a problem for the 24–40-kg sheep used in this study, but such a volume-to-weight ratio might produce hyperinflation of the alveoli in larger sheep.

To understand the significance and limits of the results of this study, several physiologic characteristics of sheep need be pointed out. In sheep, a major difference from humans is seen in the erythrocytes. Sheep not only have low Na-K pump activity, but also have relatively lower blood hemoglobin concentrations, higher P-50 values, lower 2,3-DPG levels, and a higher body temperature.[20–21] These differences must be taken into account when analyzing and comparing hemodynamics and oxygen transport in sheep and humans.[22] For example, actual PaO_2 at the sheep's body temperature (39.5–40 C) is usually 7–12 torr higher than the values obtained from blood gas analyzers with the electrode set at 37 C. Sheep also have very low plasma cholinesterase activity.[23] Interestingly, succinylcholine chloride did not have a prolonged effect in the study sheep.

Stephenson et al.[12] have suggested that the severity of smoke inhalation injury is dose-related, but physiologic measurements of dose responsiveness have not been made except for a mortality study in rats.[6] The sheep model of smoke inhalation injury used in these studies is reproducible and manifests dose responsiveness of hemodynamic and pulmonary variables that are most distinct at 24 hours. The lesser number of sheep studied at 72 hours and the narrower range of smoke doses used in the sheep studied at 72 hours may account for the poorer correlations noted at that time.

Mortality at 24 hours was well approximated by the logistic model (mortality = exp(y)/(1 + exp(y)), where $y = 0.535x - 7.865$ and x = number of smoke dose by units). This logistic model predicts mortality of 0.19% and 0.94% for 3 and 6 units of smoke exposure, respectively. Although all sheep given those doses of smoke were sacrificed after physiologic measurements at 24 or 72 hours, the clinical condition of all sheep was consistent with recovery from the inhalation injury and survival. In the sheep exposed to 6 units of smoke, none of the physiologic variables measured at 72 hours showed further deterioration from values measured at 24 hours after smoke exposure. Histologically, tracheal epithelium examined 72 hours after 6 units of smoke exposure showed metaplasia, suggesting early healing. These physiologic and histologic findings suggest that damage from 6 units of smoke is reversible. On the other hand, a 9-unit or greater dose of smoke caused progressive changes resulting in much higher mortality and further deterioration in lung function by 72 hours after exposure. Histologic changes in those sheep were also progressive; the airway epithelium showed further deterioration and congestion and atelectasis of the lung were more severe at 72 hours. The parenchymal changes were most distinct in dependent areas of the lung. This accumulation of occlusive exudate in dependent airways is probably related both to the effect of gravity and to the loss of effective normal elimination of exudate by ciliary action and coughing.

The dose-response patterns of selected physiologic indices were analyzed using the data at 24 hours after smoke exposure. Four patterns were observed (Fig. 11): (1) No apparent smoke dose effect, as exemplified by TPRI. (2) An apparent threshold effect, *i.e.*, poor linear correlation with dose ($r^2 < 0.20$), but significant change at 12-unit and/or 15-unit doses and no significant difference between those two groups: pH, peripheral vascular resistance index (PVRI), and right ventricular stroke work index (RVSWI). (3) A linear relationship (0.20

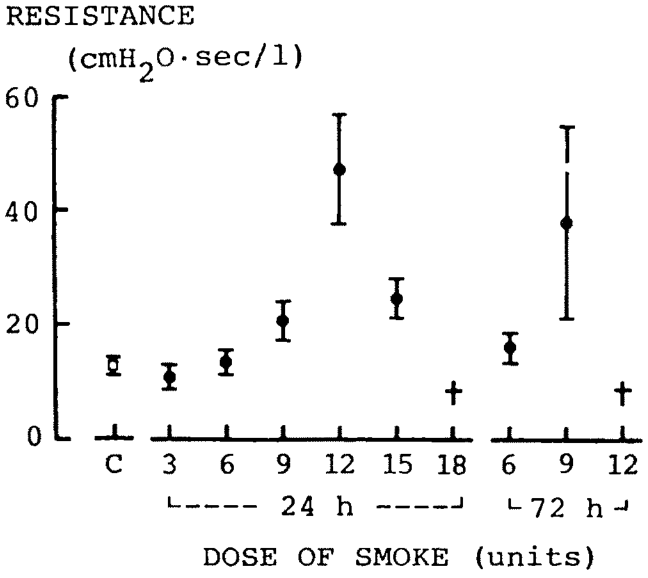

FIG. 9. Pulmonary resistance (PR) of each group. PR was calculated by the following equation: PR = (mouth pressure − intrapleural pressure)/flow rate. Mouth pressure means pressure at the connection of respiratory circuit and tracheal tube. PR includes airway resistance plus pulmonary tissue resistance.[28]

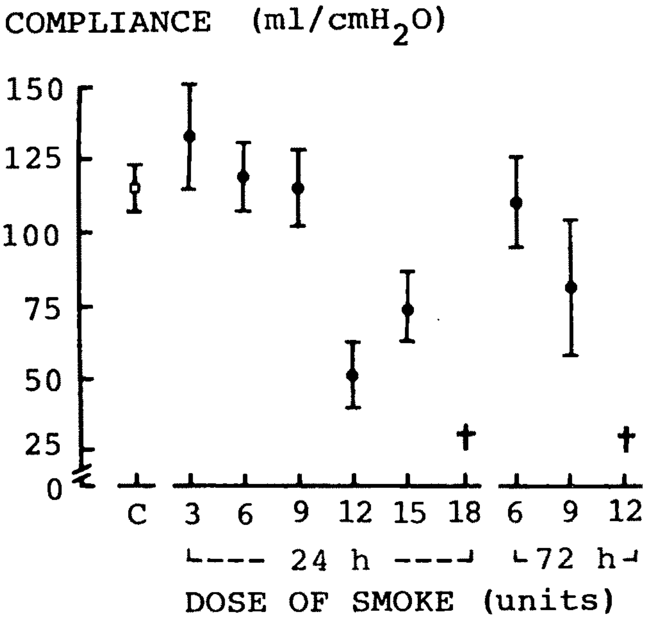

FIG. 10. Static compliance of each group. Static compliance was calculated from the following equation at end-inflation: Compliance = volume change/transpulmonary pressure. Change in compliance was a mirror image of that of pulmonary resistance.

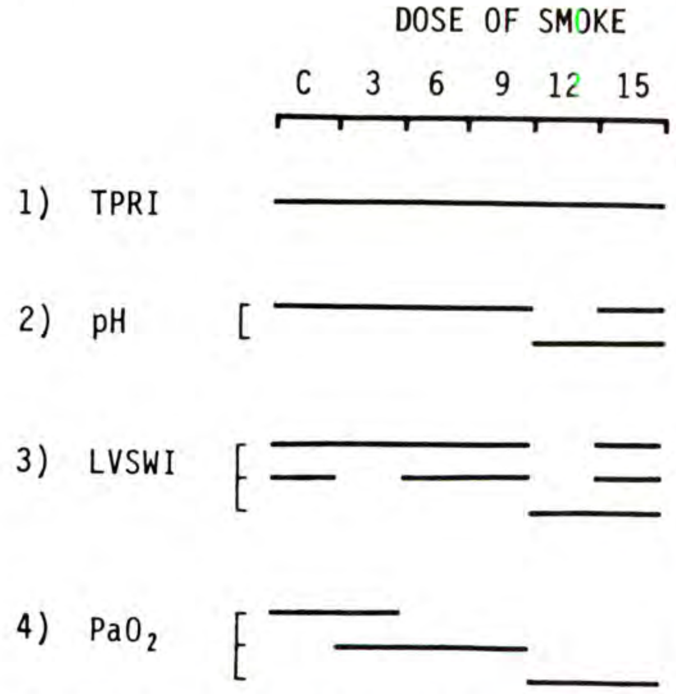

FIG. 11. Four patterns of response in physiologic indices at 24 hours after smoke exposure. Multiple comparisons by the Student-Newman-Keuls multiple range method are described by the underlining method. Groups underlined by the same line are not distinguishable from one another. Typical examples of the four patterns are shown. (1) No apparent smoke dose effect. (2) An apparent threshold effect. (3) A linear relationship ($0.20 < r^2 < 0.40$) over at least a portion of the smoke dosage range. (4) A good linear relationship ($r^2 > 0.40$) over the entire range of doses of smoke. See text for details.

$< r^2 < 0.40$) over at least a portion of the smoke dosage range: $PaCO_2$, PR, static compliance, lung water, LVSWI, and CI, where LVSWI = between 3 and 15 units and CI = between 6 and 15 units. (4) A good linear relationship ($r^2 > 0.40$) over the entire range of doses of smoke: PaO_2 ($r^2 = 0.646$), mBP ($r^2 = 0.439$), and mPAP ($r^2 = 0.407$), where mBP = between 3 and 15 units.

TPRI was maintained within the normal range in all surviving sheep, suggesting that the TPRI is well protected by homeostatic mechanisms and is not an index of the severity of inhalation injury. Indices showing threshold changes (pH, PVRI, and RVSWI) also appear to be well maintained until a severe insult is incurred. Changes in these indices are indicative of a significant smoke inhalation injury. Once a threshold level was exceeded, no significant further change in these physiologic indices was noted in the 15-unit group compared with the 12-unit group. Indices that manifested the third or fourth patterns showed moderate to good correlation between the number of units of smoke and magnitude of change.

For some variables, a significant difference from the control level was not seen (CI) nor was observed only after exposure to 12 units of smoke ($PaCO_2$, LVSWI, PR, static compliance, lung water, mBP, and PAP) when assessed by analysis of variance. PaO_2 showed the highest correlation coefficient ($r^2 = 0.646$), but a significant difference from the control level was observed only in groups exposed to 9 units of smoke or more. The dose-response curve of PaO_2 (Fig. 7) and the fact that changes of most of the cardiopulmonary indices became significant only after 12-unit exposure suggest that the dose-response curve is sigmoid in shape rather than linear, and that the steep portion of the curve is located between 9 and 12 smoke units (Fig. 12). The steep portion of the curve might also be approximated by curved linear (polynomial) functions, reflecting the progressive nature of such injury. Stephenson et al. pointed out that, by inference from the literature, there is no variable to reliably predict lung injury due to smoke inhalation.[12] That failure may be related to the sigmoid nature of the dose-response curve suggested by this study. To describe the sigmoid curve precisely, it will be necessary to assess the physiologic response over a wide range of inhalation injury severity. Several of the indices examined in this

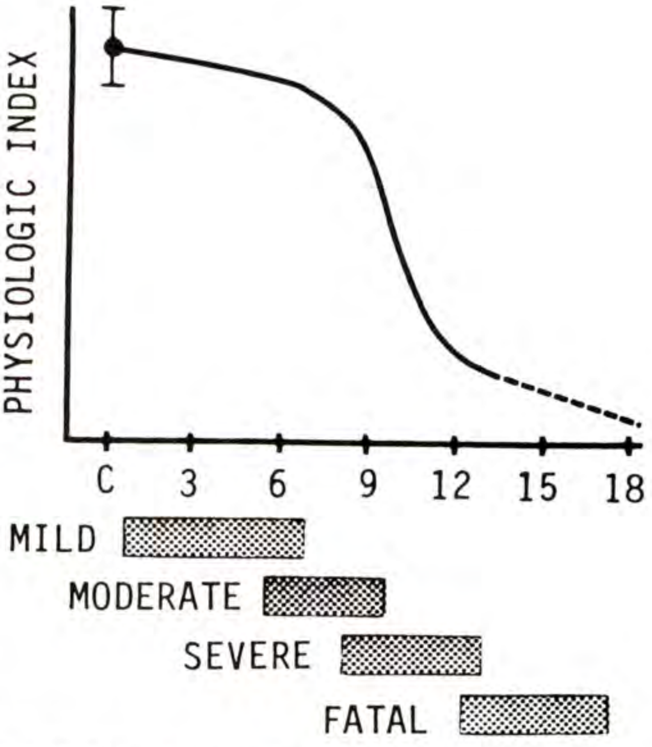

FIG. 12. Schematic presentation of dose-response curve of sigmoid nature and grading of smoke inhalation injury. Ordinate represents physiologic indices and abscissa shows doses of smoke in units. Statistical significance is not detectable at doses below 9 units. Substantial change occurs between 9 and 12 units. The plateau on the right side (shown as an interrupted line) is not clearly observed because those higher doses are fatal. The bars indicate the grading of smoke inhalation injury. See text for details.

study do not appear to be sensitive indicators of injury severity since they were not significantly altered by nonlethal doses of smoke.

Although others have reported no significant changes in PAP after smoke inhalation and have attributed pulmonary edema in such models to increased capillary permeability,[11] we observed a significant increase in PAP in sheep exposed to high doses (12 and 15 units) of smoke (Table 1). Judging from the mortality in the sheep studied by Herndon et al.[11] (13 of 27 at 72 hours), that severity of inhalation injury corresponded to little more than that caused by 9 units of smoke in our study. The change in PAP that we observed was modest until the smoke dose exceeded 9 units, above which it increased greatly. The parallelism of changes in PAP and extravascular lung water volume in the current study suggests that elevation of intravascular pressure may contribute to pulmonary edema after smoke inhalation injury.

The effect of inhalation injury on extravascular lung water volume is unclear. Markedly different thermal-dye measurements of extravascular lung water volume have been reported.[24,25] As an explanation of the discrepancies, Prien et al. have recently reported that pulmonary edema of smoke inhalation was undetectable by indicator-dilution technique in a sheep model.[26] That finding may reflect differences between patients with burns and inhalation injury and experimental models with smoke inhalation alone. In laboratory studies, including our study, the animals did not have cutaneous burns and they did not receive large volumes of resuscitation fluid. Since the composition of administered fluids affects lung water accumulation in burn patients,[27] differences in resuscitation regimens may account for some of the reported differences in lung water measured in burn patients. We showed in this study that lung water change was not significant until the severity of inhalation injury reached a certain level, *i.e.,* 12 units of smoke, which caused 100% mortality within 72 hours. This indicates that, apart from any insensitivity of the indicator-dilution methods, extravascular lung water volume may not be increased in less severe inhalation injury.

It is important to identify the severity as well as the presence of inhalation injury. In this study, PaO_2 showed the best dose-response relationship, and although it appears to be the most reliable index for estimating the severity of smoke inhalation injury, PaO_2 changes are not specific to such injury. It may be more useful to grade smoke inhalation as mild (3–6 units), moderate (6–9 units), severe (9–12 units), and invariably fatal (over 12 units) (Fig. 12). Mild smoke inhalation injury did not cause death by itself and all the physiologic indices remained normal. In some animals with mild injury, no tracheal pseudomembrane formation was evident and when present was minimal. Diagnosis of smoke inhalation injury of this degree would be difficult without histologic examination at an appropriate time. Moderate injury was associated with a mortality of 30% by 72 hours. Pseudomembrane formation in the major airways was always evident but many physiologic indices still did not change significantly. Severe inhalation injury caused 10–14% mortality by 24 hours and 30–100% mortality by 72 hours. A thick pseudomembrane formed in the airways and physiologic indices showed significant changes. The variability of changes noted in the various indices may be attributable to the sigmoid shape of the dose-response curve. Invariably, fatal injury caused total loss of airway epithelium and 100% mortality. Although this grading is based on an experimental model of smoke inhalation without cutaneous burns, a similar grading for smoke inhalation in burn patients may be useful in evaluating the severity of smoke inhalation and assessing treatment outcome. This dose-responsive sheep model can now be used to determine the pathogenesis of inhalation injury, to assess the effect of associated burn injury, and to evaluate the effectiveness of therapeutic interventions.

Acknowledgments

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Diagnosis of Varicocele and Postoperative Evaluation Using Inguinal Ultrasonography

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Ultrasonographic real-time imaging and measurements of spermatic veins in the inguinal canal were evaluated in two groups of patients: 20 young men with varicocele and 18 controls. Examinations were performed with the patient in an upright relaxed position, and performing the Valsalva maneuver. The increase in diameter of the main vein during Valsalva maneuver was considered to quantitatively represent venous reflux. The data obtained were correlated with pre- and postoperative clinical findings. This method of evaluation proved to be a useful noninvasive diagnostic modality for detecting varicocele and for assessing treatment results. On the basis of venous diameters and reflux values, a classification of varicocele is proposed. Such an objective method of grading would eliminate the subjective impression and interpretation factors of the examiner.

DIAGNOSIS OF VARICOCELE is important since it has been found in as many as 21–39% of men attending infertility clinics.[1] Small varicoceles may have the same impact on fertility as large lesions.[2] Recognition of the dilated veins is usually made by physical examination. The lack of accuracy of diagnosis based only on visualization and palpation is obvious and many small lesions may escape detection.

Varicoceles are commonly classified as small, moderate, or large, according to a subjective grading of venous size and reflux.[2] Retrograde venography is an objective and precise diagnostic method, but it is invasive and cannot be used for screening. More recently, several noninvasive methods have been proposed for improving the diagnosis of varicocele, mainly for small lesions in which recognition of venous dilation and reflux is problematic. A recent multicenter trial organized by the World Health Organization (WHO) reported satisfactory results using a combination of Doppler sonography and contact scrotal termography.[3]

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The use of ultrasonography for scrotal vein imaging has been scarcely reported in the radiologic literature[4-6] and did not have impact on current clinical evaluation of varicocele. Sonography was not even mentioned in the WHO's multicenter study as an actual diagnostic modality.

The current prospective controlled study was done to assess the value of real-time ultrasonography of spermatic veins at the inguinal canal level, for diagnosis of varicocele and for postoperative evaluation.

Materials and Methods

The left spermatic cord veins were detected by inguinal imaging ultrasonography in two groups of patients: (1) varicocele group: comprising 20 young men with clinically diagnosed left varicocele (age range: 16–23 years, mean age: 19 years), and (2) control group: comprising 18 young men referred to surgery because of minor disorders unrelated to the genital area. Absence of genital abnormalities and, specifically, varicocele was confirmed by physical examination. Age range was 16–38 years, mean age was 25 years.

Imaging of the Left Spermatic Cord Veins

The examinations were performed using a B-mode gray-scale ultrasound with 5-MHz transducer (Picker International Inc., GmbH, München, West Germany) and a Dynex Elscint with 5-MHz and high-resolution 10-MHz transducer (Elscint Ltd., Haifa, Israel).

In both groups the patients were examined in an upright position. Imaging of the venous plexus was obtained by direct contact with the skin in the inguinal

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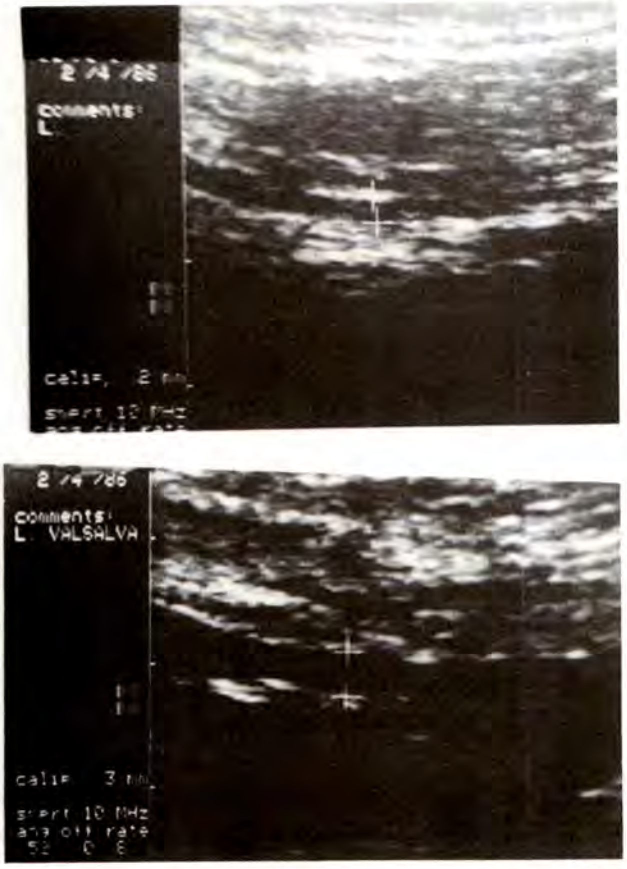

FIG. 1. Longitudinal sonogram of left spermatic cord at the inguinal canal level (10-MH transducer). Top: relaxed standing position; diameter of the dominant vein: 2 mm. Bottom: during Valsalva maneuver, the dominant vein dilated to 3 mm. Diagnosis: small varicocele, reflux of 1 mm.

region. The transducer was positioned for longitudinal axis scanning of the spermatic cord in the inguinal canal, parallel to the medial half of the inguinal ligament. Scanning was performed with 45° inclination of the transducer. The diameter of the dominant draining vein was measured with the patient relaxed and while performing the Valsalva maneuver. Measurements in the varicocele group were performed before operation and 3 months after operation. The patients were operated on by the classic retroperitoneal high ligation technique.

TABLE 1. *Mean Diameters of Dominant Veins and Venous Reflux in the Left Spermatic Cord*

	Varicocele Group		
	Before Operation	After Operation	Control Group
Diameter during relaxation (mm)	4.5	2.0	2.2
Diameter during Valsalva maneuver (mm)	5.7	2.8	2.7
Reflux (increase in diameter during Valsalva) (mm)	1.2 ($p < 0.001$)*	0.8 (NS)	0.5 (NS)

* Statistical analysis by Student's t-test.

We calculated the difference between the main diameter of the dominant draining vein during Valsalva maneuver, and in relaxed upright position. This value was considered as the numeric expression of venous reflux into the pampiniform plexus. The ultrasonographic measurements of the varicocele and control groups were compared.

Results

Longitudinal sonograms of the left spermatic cord permitted good visualization of the venous channels. Particularly clear imaging, even in small lesions, was obtained by using the high-resolution 10-MHz transducer. When the spermatic cord was scanned at the level of the inguinal canal, a dominant draining vein could be identified and its diameter measured. The main vein was accompanied by smaller channels running longitudinally, the complex constituting the pampiniform plexus (Fig. 1).

Varicocele Group

Preoperative values. The mean diameter of the dominant veins in the left spermatic cord during normal respiration in erect position was 4.5 mm. The mean diameter increased to 5.7 mm during Valsalva maneuver. The difference (numeric expression of venous reflux) of 1.2 mm was significant ($p < 0.001$) by the Student's t-test.

Postoperative values. During relaxation the mean venous diameter was 2 mm, and during the Valsalva maneuver was 2.8 mm. The difference of 0.8 mm was not significant.

Control Group

The mean diameter of the main veins during relaxation was 2.2 mm. When the patients performed the Valsalva maneuver, the mean diameter increased to 2.7 mm. The numeric expression of venous reflux of 0.5 mm was not significant.

Table 1 summarizes the measurements of mean diameters of the dominant veins and of venous reflux in the left spermatic cord in both groups.

The varicocele group was further divided into three subgroups according to the size of the main left spermatic veins (Table 2): (1) Small varicocele: mean diameter of main veins in relaxed standing position ranged between 2.5 and 4.0 mm. During Valsalva maneuver there was an increase of about 1.0 mm. (2) Moderate varicocele: mean diameter of main veins oscillated between 4.0 and 5.0 mm and during the Valsalva maneuver increased 1.2–1.5 mm. (3) Large varicocele: mean dominant vein diameter during normal respiration was greater than 5.0 mm, and during the Valsalva maneuver there was an increase of more than 1.5 mm.

Discussion

Our results indicate that varicocele can be accurately diagnosed by ultrasonograhic imaging. High-resolution transducers can reveal even small varicoceles. Current methods of diagnosis, namely physical examination, termography, or Doppler stethoscope, are largely dependent on the subjective impression and interpretation of the examiner, yielding imprecise and noncomparable data. This situation does not permit conduction of truly reproducible studies, and no uniform classification can be used.

Previous reports showed the ability of ultrasonography for imaging and even measuring the diameter of normal and dilated scrotal veins.[4–6] We performed the measurements of the spermatic cord veins at the inguinal level. The fact that the average diameter of any venous network increases centripetally explains why the values of our control group were slightly higher than the 2 mm described as the upper normal limit in previous reports. We consider the spermatic cord veins in the inguinal canal as the appropriate evaluation site because of their longitudinal alignment in contrast to the convoluted and irregular venous arrangement at the scrotal level.

In the varicocele group the mean diameter was 4.5 mm in relaxation and 5.7 mm during the Valsalva maneuver. These values are again consistent with previous publications, which found scrotal veins of 5–6 mm diameter in varicocele patients. It seems that these values of normal and pathologic calibers of veins can be accepted as guidelines to sonographic diagnosis of varicocele (Table 1). The difference between the mean diameters of the dominant draining vein during Valsalva maneuver and in relaxed standing position ranged between 1.0 and 1.7 mm. These values were objective representatives of the venous reflux into the pampiniform plexus. When we consider the measurements performed in the varicocele group before and after operation, it is striking that the postoperative values became similar to those obtained in the control group. The pre-operative reflux was highly significant and became nonsignificant after surgical treatment (Table 1). These data suggest that ultrasonography can be useful in the follow-up of treatment results, giving objective definition of success or failure.

TABLE 2. *Suggested Classification of Varicocele*

	Normal Values	Small	Moderate	Large
Dominant vein diameter (standing relaxed) (mm)	0.5–2.5	2.5–4.0	4.0–5.0	>5.0
Reflux (mm)	0.5–1.0	1.0–1.2	1.2–1.5	>1.5

The ability to provide measurements data is one of the main advantages of this noninvasive method. Measurements of spermatic vein diameter and of venous reflux enabled us to classify varicoceles as small, moderate, and large (Table 2). This "quantitative" ultrasonographic classification is more precise and comparable than previous classifications based on physical examination only.

In conclusion, ultrasonographic imaging and measuring of the spermatic cord veins at the inguinal canal level can be recommended as an accurate screening procedure for: (1) diagnosis of varicocele, (2) clinical classification, and (3) assessment of treatment results. However, further studies are necessary to determine the sensibility of this method for detecting very small or subtle varicoceles.

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Origin of the Right Pulmonary Artery from the Ascending Aorta

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Origin of the right pulmonary artery from the aorta is a congenital malformation usually associated with serious symptoms in the first year of life and characterized by a poor prognosis. Sixty-five patients with this disorder have been reviewed in the literature, and 95% presented during the first year with signs of congestive heart failure. All had cardiomegaly by radiographic and electrocardiographic examination. An accurate diagnosis was established by cineangiography, and associated cardiovascular anomalies were present in 85%. Origin of the *right* pulmonary artery from the ascending aorta is much more common than origin of the left pulmonary artery from this vessel (8 to 1). Twenty-three patients were managed without operation with a 30% 1-year survival rate. Among those patients managed surgically, the survival rate was 84% at 1 year. It is now clear that operation should be done as early as possible to prevent irreversible changes occurring in the pulmonary arterial vasculature since microscopic features of pulmonary hypertension have been seen during the first month of life. One patient was operated on at 5 months with correction of the deformity. The pulmonary arterial pressure decreased to normal after operation. This child is now asymptomatic and his 10-year postoperative follow-up is the longest found in the literature.

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ORIGIN OF A PULMONARY ARTERY from the ascending aorta is a rare congenital malformation of the great vessels that is usually fatal without early surgical correction. The first patient, a 25-year-old woman, was reported by Fraentzel in 1868 and died of congestive heart failure.[1] Postmortem examination revealed an aortopulmonary window and origin of the right pulmonary artery from the ascending aorta. It has been emphasized that there are at least three different cardiovascular malformations that have been given the same terminology, including: (1) origin of the right pulmonary artery (RPA) or left pulmonary artery (LPA) from the ascending aorta, (2) absence of the proximal portion of the RPA or LPA with distal RPA or LPA supplied *via* a patient ductus arteriosus (PDA), and (3) absence of a proximal pulmonary artery branch with the distal RPA or LPA supplied by an aortopulmonary collateral other than a PDA.[2] The latter two conditions differ from the first in embryologic development and physiologic behavior. When the RPA or LPA originate from a PDA or collateral arteries, the pressure in the vessel is often elevated but less than systemic pressure, whereas in aortic origin of the pulmonary artery, the pressure is at the systemic level.

Physiologically, the alteration creates a large left-to-right shunt from the aorta to the pulmonary circulation and then to the left atrium. The contralateral lung is therefore subjected to the entire right ventricular output in addition to flow contributed by associated anomalies, *e.g.*, PDA, atrial septal defect (ASD), ventricular septal defect (VSD), or aortopulmonary septal defect, which have been present in greater than 60% of previous reports. The pulmonary artery pressures on the contralateral side are elevated.

Clinical Presentation

Two patients with origin of the RPA from the ascending aorta have been seen in this medical center. The first patient died in the first month of life of congestive heart failure. The postmortem findings included origin of the RPA from the ascending aorta as well as a small PDA.[3] The second patient was a 7-pound male infant and product of an uncomplicated pregnancy, labor, and delivery to a 20-year-old primapara. Examination was described as normal at birth and the infant was discharged on the second day of life. During his first month, the child tired

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easily with feeding and occasionally became short of breath with activity. At 1 month of age a holosystolic murmur was heard, and the child was referred to the Duke University Medical Center for further evaluation.

On physical examination, he was a normal-appearing noncyanotic white male infant with a regular pulse of 180 beats per minute, respiratory rate of 44 per minute, and blood pressure of 110/52 mmHg. The lungs were clear, the precordium was active, and a thrill was noted along the left midclavicular line. Auscultation revealed a normal S1, widely split S2, and a III–IV/VI holosystolic murmur along the left sternal border and at the apex. There were no diastolic murmurs. The remainder of the physical examination was normal.

Chest films were significant for mild cardiomegaly and bilateral prominence of the pulmonary vasculature, right greater than left (Fig. 1). The electrocardiogram showed bilateral ventricular hypertrophy. At 2.5 months of age, cardiac catheterization, including biplane cineangiography, was performed. The significant findings included aortic origin of the RPA and a patent foramen ovale without a significant shunt. The ductus arteriosus was described as not patent. LPA pressure was two-thirds systemic, and the ventricular septum was intact. Pressure and oxygen saturation data are shown in Table 1. After catheterization, the patient was treated medically with digoxin, and over a 6-week period symptomatic improvement was evident. Failure to thrive at approximately 5 months of age led to performance of a corrective surgical procedure.

The operation was performed through a median sternotomy (Figs. 2A–C). The pericardium was opened and with leftward retraction of the aorta, the RPA was seen to arise from the posterior aspect of the ascending aorta. At its origin, the RPA measured 12 mm in diameter. A 4-mm ductus arteriosus was noted to be patent and was closed. A partial occlusion clamp was placed on the posterior portion of the ascending aorta at the origin of the RPA. Another arterial clamp was placed distally on the RPA. The RPA was divided at its origin and the aortic defect was oversewn. A 12-mm woven Dacron graft was preclotted and anastomosed to the distal RPA. A partial occlusion clamp was placed on the right lateral aspect of the main pulmonary artery (MPA) just distal to the pulmonary valve. The graft was then anastomosed to the MPA with a continuous suture of 5-0 Ticron. Immediately after opening the graft, the systolic pressure in the RPA was 20 mmHg and was 22 mmHg in the LPA. On the ninth postoperative day, a ventilation/perfusion scan revealed bilateral pulmonary flow *via* the MPA. Digoxin therapy was continued for approximately 3 months and then discontinued.

One year after operation the patient was asymptomatic and had resumed normal growth. Follow-up catheterization performed in February 1977, showed mild proximal stenosis of the RPA, a patent foramen ovale without significant interatrial shunt, and pressure and oxygen saturation data as shown in Table 1. The electrocardiogram (EKG) at that time showed mild right ventricular hypertrophy, and a ventilation/perfusion scan was considered normal.

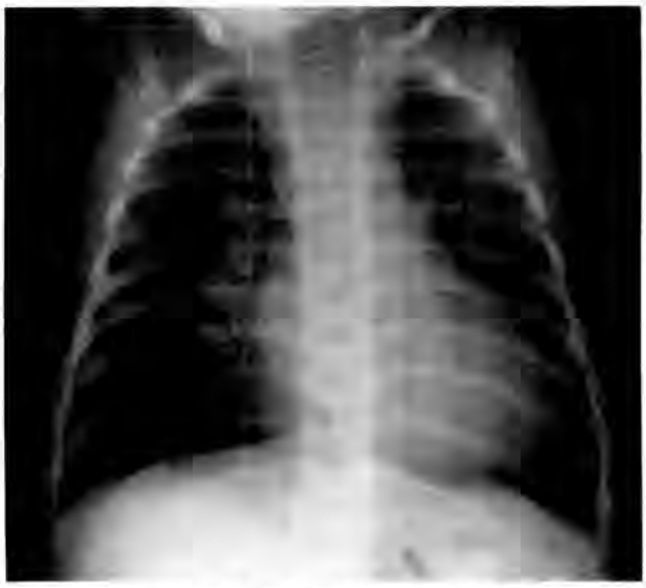

FIG. 1. Preoperative chest film showing mild cardiomegaly and bilateral prominence of the pulmonary vasculature most prominent on the right side.

TABLE 1. *Cardiac Catheterization Results*

	Preoperative		Postoperative	
Site	Pressures (mmHg)	Oxygen Saturation*	Pressures (mmHg)	Oxygen Saturation*
SVC		60		73
IVC		61		74
RA	4	59.5	8	72
RV	76/8	61	46/8	72
MPA		58.5	42/12	
LPA	72/30	57	33/14	72
RPA	108/50	90	25/12	73.5
LA	6			96
LV	108/52	90	120/4	96
Aorta	108/52			
RPV		94		
PCWP	14			

* $F_IO_2 = 0.21$.
SVC = superior vena cava.
IVC = inferior vena cava.
RA = right atrium.
RV = right ventricle.
MPA = main pulmonary artery.
LPA = left pulmonary artery.
RPA = right pulmonary artery.
LA = left atrium.
LV = left ventricle.
RPV = right pulmonary vein.
PCWP = pulmonary capillary wedge pressure.

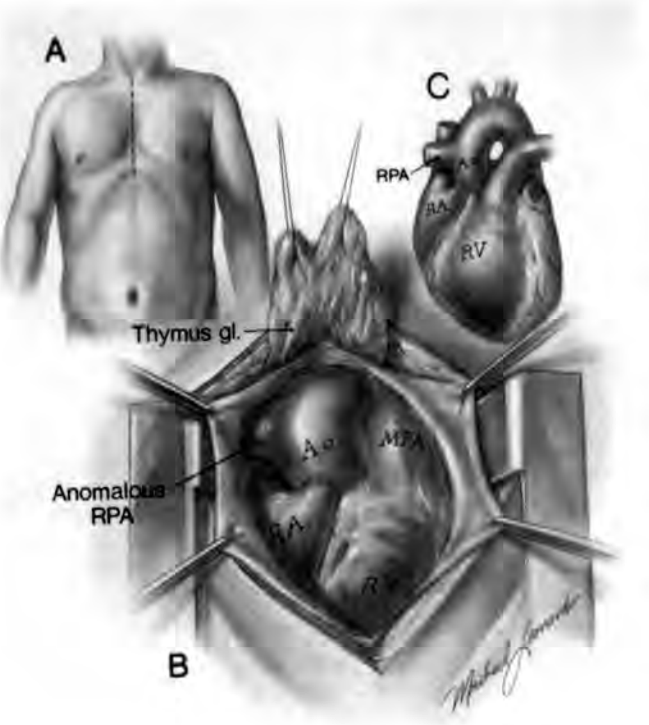

FIG. 2A. A: Median sternotomy. B: The pericardium is opened. C: The right pulmonary artery is seen as it arises from the ascending aorta.

Since 1977, the patient has maintained normal growth and development with no symptoms or signs of congestive heart failure. The EKG has become normal since operation and the chest films reveal a normal cardiothoracic ratio. The lung fields indicate a right-sided oligemia with compensatory left-sided hyperemia (Fig. 3). The patient had development of reactive airway disease at age 5, but has responded to medical therapy and has had no bronchospastic episodes for the past 2 years.

In 1983, a radionuclide angiogram was performed, revealing 39% of the right ventricular output distributed to the right lung, and 61% to the left lung. Radionuclide angiogram in 1986 showed delayed flow to the right lung and normal ventricular function. A ventilation/perfusion scan was performed, which revealed that 14% of the right ventricular output perfused the right lung, whereas 86% perfused the left side (Fig. 4). The ventilation scan was normal.

Review of the Literature

Sixty-five patients with true origin of the RPA from the ascending aorta have been reported in the English literature.[1-44] The distribution was males (64%) and females (36%). Almost all patients (95%) presented during infancy with signs of congestive heart failure, including respiratory distress, tachycardia, and failure to thrive. All those examined had cardiac murmurs, and 41% either presented with or had a history of cyanosis. One patient had hemoptysis.

In the 48 patients in whom chest films were reported, cardiomegaly was present as well as abnormalities in pulmonary vascularity. Bilateral increased flow was noted in 65% and increased flow on the right *versus* the left occurred in 35%. There were no instances of prominent pulmonary vascularity on the left side only. EKGs (48 patients) showed nonspecific findings of right ventricular hypertrophy (59%), left ventricular hypertrophy (6%), or biventricular hypertrophy (35%). Aortic origin of the RPA associated with PDA were in all three electrocardiographic categories. Arterial blood oxygen saturation was normal in those patients without a reason for substantial reduction in gas exchange, *i.e.*, pulmonary edema or bronchopneumonia. Two-dimensional echocardiography was performed in some patients and the short-axis viewing from the suprasternal notch position accurately demonstrated the anomaly in the aorta.

Preoperative or premortem diagnosis by cardiac catheterization was obtained in 73% of patients. Preopera-

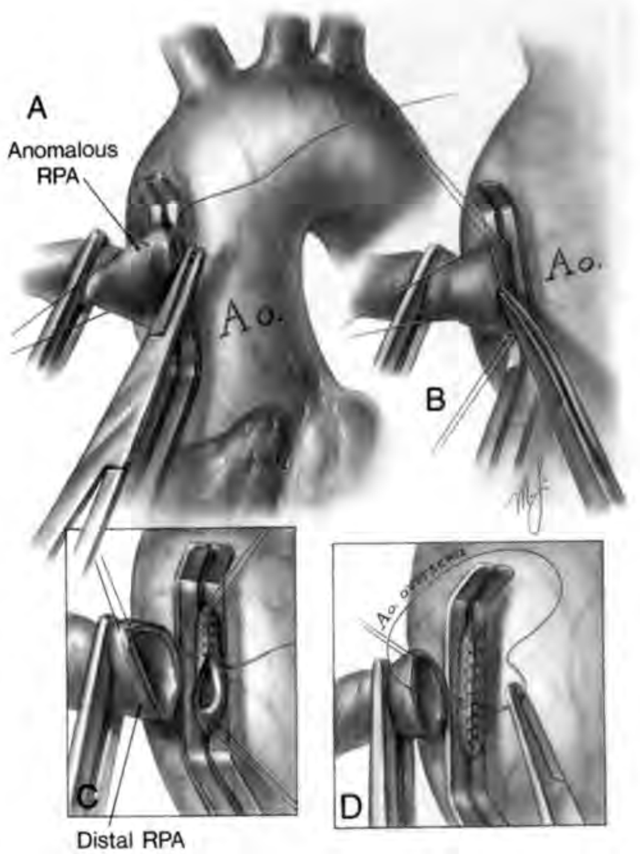

FIG. 2B. A: A partial occlusion clamp (Satinsky) is placed at the origin of the right pulmonary artery. B: The right pulmonary artery is divided at its origin. C, D: The aortic defect is oversewn.

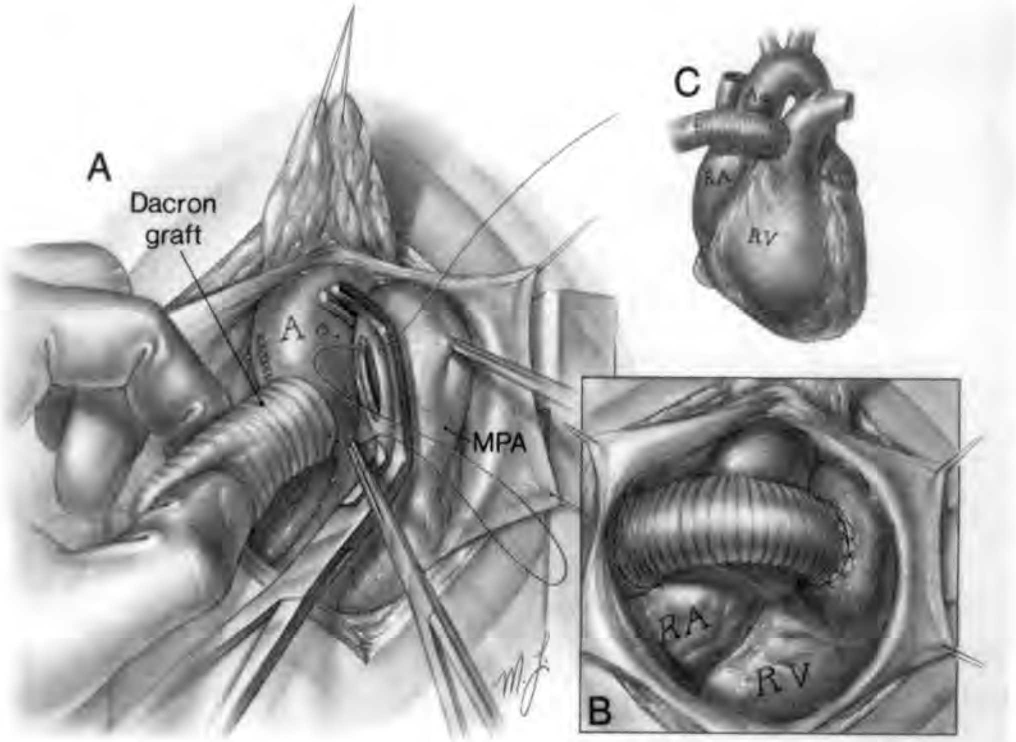

FIG. 2C. A: A partial occlusion clamp is placed on the right lateral aspect of the main pulmonary artery. A preclotted woven Dacron graft is anastomosed to the main pulmonary artery. B: The graft is then attached to the distal right pulmonary artery. C: The completed repair.

tive misdiagnosis at catheterization occurred in three patients. In the first patient, a cineangiogram was not performed,[4] and the preoperative diagnosis was an isolated PDA. Ligation of the PDA was performed with subsequent deterioration of the patient, leading to death on the day of operation. A diagnosis of aortic origin of the RPA was made at autopsy. In the other two patients, abnormal origin of the RPA was *not* noted on cineangiogram before operation. After finding the anomaly during operation, the films were reviewed and the lesion was identified retrospectively.[44]

The most common anomaly associated with ascending aortic origin of the RPA was PDA (68%), followed by aortopulmonary septal defect (15%), hypoplastic or interrupted aortic arch (11%), patent foramen ovale (8%), ventricular septal defect (8%), atrial septal defect (8%), coarctation of the aorta (5%), tetralogy of Fallot (3%), and tricuspid atresia (2%). There were no associated anomalies found in 15% of patients (Table 2). A syndrome of aortopulmonary septal defect (APSD), hypoplastic or interrupted aortic arch, intact ventricular septum, PDA, and aortic origin of the RPA has been reported in nine patients.[41–44]

Systemic pressures in the RPA were found in all patients who had cardiac catheterization. LPA pressures were greater than or equal to two-thirds systemic pressure. Lung biopsy at operation or pathologic section at postmortem examination was obtained in 23 patients. Normal findings were present in five patients (age at examination: 3 days to 2 months). Intimal changes were present in eight patients (age at examination: 1 month to 21 years). Medial hypertrophy was seen in 16 patients (age at examination: 1 month to 21 years). In the major-

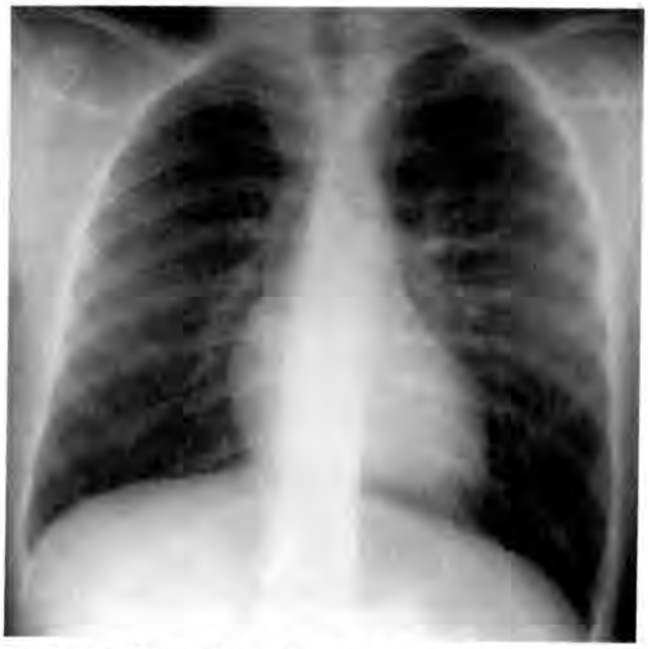

FIG. 3. Chest film at 10-year follow-up with normal-sized heart and diminution of right hilum and right pulmonary arteries. The left hilum and left pulmonary arteries are prominent.

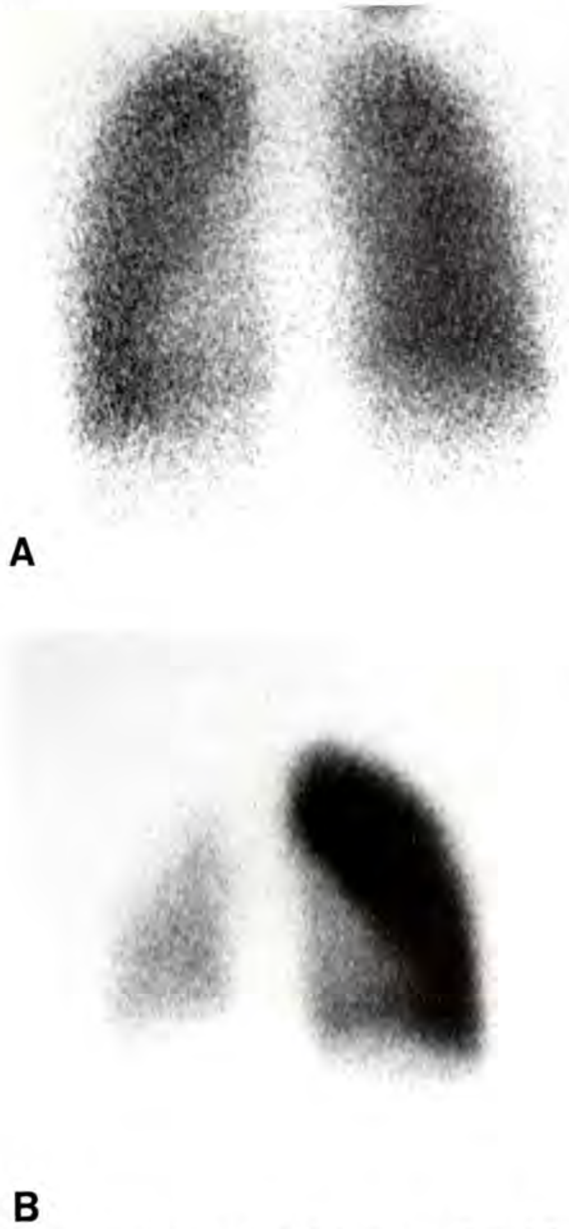

FIG. 4A and B. Ventilation/perfusion scan at 10-year follow-up. *A.* Ventilation scan (posterior view), which is normal. *B.* Perfusion scan (anterior view) showing reduced flow to the right lung.

ity of patients (67%) in whom pathologic changes were present, the findings were bilaterally symmetrical. The others had various degrees of medial and intimal abnormalities that occurred asymmetrically. It has been suggested that the differential development of pulmonary obstructive vascular disease is related to the disparate oxygen content of blood delivered to the affected side.[23] Nonparametric analysis of age *versus* onset of pathologic changes was significant to $p < 0.001$. Nonparametric analysis using the Kolmogorov-Smirnov Two-Sample Test was required for analysis of these data because of the effect two long-term survivors had on means and standard deviation, leading to failure of parametric analysis. Although both intimal and medial changes were observed in patients at 1 month of age, medial hypertrophy alone was seen in many patients 1–6 months of age and appeared to precede development of intimal hyperplasia. Due to the small sample size and wide range of ages, this did not achieve statistical significance.

Twenty-three patients were managed medically or had no treatment. The natural history without operation is illustrated in Figure 5. Thirty-five per cent died in the first month of life and 70% died by the age of 1 year. There were only four long-term survivors (17% living beyond 10 years) in the nonsurgical group. One patient with aortic origin of the RPA, tricuspid atresia, VSD, and hypoplasia of the right side of the heart, was surprisingly doing well with minimal exercise intolerance at the age of 9.[22] In this patient, anomalous origin of the RPA was the major source of pulmonary blood flow. The other long-term survivor was a 21-year-old woman, with an associated PDA, who was deemed inoperable at age 18 years secondary to "irreversible" pulmonary hypertension.[21] At that time, the patient had generalized cyanosis accompanied by exercise intolerance and episodes of hemoptysis. Right-to-left shunting was present at the level of the ductus arteriosus. She was attending college and her clinical status was stable at age 21 years. There were two long-term survivors with aortopulmonary septal defect, PDA, hypoplastic or interrupted aortic arch, and aortic origin of the RPA, both of whom died of profound congestive heart failure with postmortem evidence of severe pulmonary hypertension.[41,42]

Many procedures have been used to palliate or correct aortic origin of the RPA and its associated anomalies (Table 3). PDA ligation alone[4,10] and PDA ligation in association with RPA ligation[9,13] were uniformly unsuccessful and were performed early in the history of the treatment of this disorder. The first successful anatomic repair was reported by Armer et al. in 1961 with inter-

TABLE 2. *Associated Anomalies**

Defect	No. of Patients	Incidence (%)
Patent ductus arteriosus	45	68
Aortopulmonary window	10	15
None	10	15
Hypoplastic or interrupted aortic arch	7	11
Patent foramen ovale	5	8
Ventricular septal defect	5	8
Atrial septal defect	5	8
Coarctation of the aorta	3	5
Tetralogy of Fallot	2	3
Tricuspid atresia	1	2

* Some anomalies occurred in combination.

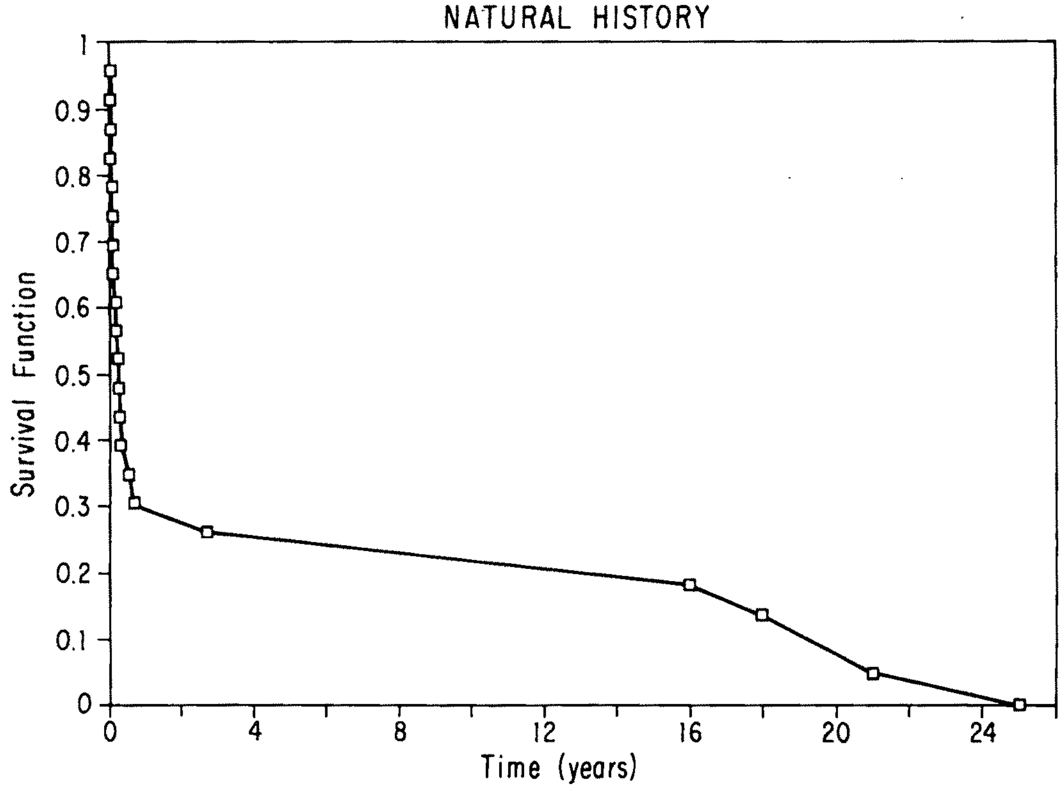

FIG. 5. Survival curve of nonoperative group (life table).

position of a Dacron graft between the RPA and the MPA (end-to-side).[5] A report by Caro et al. in 1957 of successful repair of anomalous origin of the RPA using an Ivalon interposition graft represented a patient in whom the anomalous RPA originated from the *innominate* artery.[45] The first successful primary repair was reported by Kirkpatrick et al. in 1967.[14] Both primary repair and graft interposition have been used since their respective first descriptions. Primary repair is generally reserved for those patients in whom the RPA originates from the posterior aspect of the aorta in close proximity to the MPA. When the RPA originates from the right lateral aspect of the aorta, the right hilum is often mobilized medially to allow apposition of the RPA and MPA without tension. Alternatively, interposition synthetic graft is placed either anterior or posterior to the aorta.

Three different types of primary repair have been performed, the most common (20 patients) being an anastomosis of the RPA to the MPA posterior to the aorta in an end-to-side fashion. One side-to-side repair was made in association with a VSD closure in a patient who had previous pulmonary artery banding.[18] In this patient, the aorta was clamped just proximal to the innominate artery after establishment of cardiopulmonary bypass. A vertical aortotomy was made and a right-angle clamp was passed through the orifice of the RPA. The left posterior aspect of the vessel was retracted to the left, placing it in apposition to the MPA. A side-to-side anastomosis was then performed. The origin of the RPA was closed through the aortotomy with interrupted sutures. A creative third method was performed in only one patient in whom the length of the RPA was inadequate for primary anastomosis.[29] Instead of using a graft, a modified primary repair was performed. After cardiopulmonary bypass was established and the aorta cross-clamped just proximal to the innominate artery, the anterior aspect of the aorta was incised transversly at the origin of the RPA. Under direct vision, the remaining aorta was then transected and a small cuff of posterior aortic wall around the pulmonary artery origin was excised without compromising the left coronary ostium. Adequate length for a primary end-to-side anastomosis to the MPA was provided. The aortic arch was then mobilized and subsequently reconstructed under no tension.

Correction of patients with *complex* associated anomalies is associated with a high mortality rate (60% at 1 month). Five patients with the aforementioned syndrome of APSD associated with aortic origin of the RPA have been operated on, and the techniques used have been previously described.[44]

In 25 patients, pulmonary arterial pressures were obtained before and after operation. In all patients, irrespective of age and associated anomalies, the right-sided pressures decreased after operation, although not all became normal. The age range at operation among these 25 patients was 5 days to 20 years. Normalization of

TABLE 3. *Operative Procedures and Results*

		Mortality Rate (%)	
Type of Repair	No. of Patients	1 Month	1 Year
Nonanatomic			
PDA ligation	2	50	100
PDA ligation and RPA ligation	2	100	100
Blalock Taussig shunt*	1	0	0
Total	5	60	80
Anatomic			
Primary anastomosis alone	7	0	0
+ PDA ligation	10	20	30
+ ASD closure	3	33	33
+ VSD closure, (side-to-side repair), debanding	1	0	0
Aortic cuff method	1	0	0
Interposition of Synthetic Graft			
Anterior to aorta + PDA ligation	7	0	0
Posterior to aorta	1	0	0
Posterior to aorta + PDA ligation	1	100	100
Total	31	13	16
Repairs in association with complex anomalies			
TOF repair, RV/PA conduit, primary AORPA repair	1	100	100
APSD closure, PDA ligation, repair of hypoplastic or interrupted aortic arch, repair of aorta	4	50	N/A
Total	5	60	N/A
Overall mortality rate of anatomic repair excluding patients with complex anomalies and those severely ill or moribund before operation		3.2	6.4

* Patient with Tetralogy of Fallot.
N/A = not available.
PDA = patent ductus arteriosus.
RPA = right pulmonary artery.
ASD = atrial septal defect.
VSD = ventricular septal defect.
TOF = tetralogy of Fallot.
RV/PA = right ventricle/pulmonary artery.
AORPA = aortic origin of the right pulmonary artery
APSD = aortopulmonary septal defect.

pressures after anatomic correction as a function of age was statistically tested and found to be significant using the Student's t-test ($p < 0.02$), and the nonparametric Kolmogorov-Smirnov Two-Sample Test ($p < 0.003$). The trend towards nonnormalization began in patients corrected after 4 months of age.

Follow-up of patients treated surgically ranged from birth to 5 years. Among those who had anatomic correction, all were asymptomatic even though some had persistent pulmonary hypertension. The longest postoperative follow-up study of pulmonary flow was 4 years in a patient who was corrected with a Teflon interposition graft.[21] At that time, pulmonary pressures were found to be normal and flow to lungs was bilateral and symmetrical with a 7-mmHg MPA to RPA gradient. There are no 10-year evaluations in the literature except for one of the patients reported in this study.

Embryology

Although the term "hemitruncus" has frequently been applied to the origin of the RPA from the aorta, it is not accurate since aortopulmonary septation is usually complete and the truncus arteriosus is not persistent. The term implies that the anomalous vessel arises from a common arterial trunk and therefore its use should be discouraged.

The proximal portions of the RPA and LPA arise from the most proximal portions of the sixth aortic arches, which in turn arise from the posterior aspect of the aortic sac. Two different interpretations of these developmental relationships in humans are shown in Figures 6 and 7.[46–48] The sixth aortic arches may arise on opposite sides of the aortic sac.[46] There is a leftward migration of the RPA towards the LPA and the left sixth arch. Alternatively, the RPA and LPA may initially be more closely related. This is followed by a realignment of the RPA toward the MPA, which relates directly to the origin of the LPA (Fig. 8). Sequential events in the development of the aortic arches and pulmonary arteries may be directly imaged in rodent embryos by using a method employing microradiography after microvascular injections of silver nitrate.[49] Aortic arch development in the mouse is analogous to that in humans.[49] In the mouse embryo, the RPA and LPA closely relate to the posterior aspect of the aortic sac (Fig. 8, *left*) and subsequently to the proximal MPA (Fig. 8, *right*). This work supports the earlier studies of Congdon.[47]

Two major hypotheses have been advanced to explain anomalous origin of the RPA from the ascending aorta.[24,31] In the first, origin of the RPA from the aorta is attributed to a "subnormal" migration of the RPA that leaves its origin relating to the aorta after normal truncal septation.[31] Normally, fusion of the truncal ridges results in partitioning of the truncus arteriosus into the aorta and MPA. The truncal malseptation hypothesis[49] attributes anomalous origin of the RPA from the aorta to an asymmetric division of the truncus that leaves the right sixth arch on the "wrong" (aortic) side. Schneiderman[50] attributed the anomaly to faulty timing in the simultaneous events of migration of the RPA and truncal septation.

The accuracy of these competing hypotheses can be determined only by future experimental methods. How-

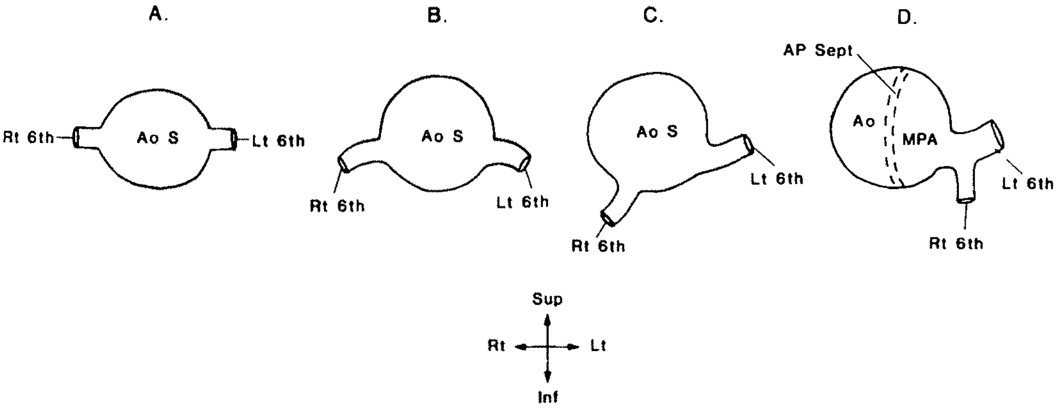

FIG. 6. Development at the pulmonary arteries (redrawn from Orts Llorca original diagrams, 1933, by permission).

ever, several reported experimental embryologic studies are relevant to an understanding of the pathogenesis of this anomaly. In Vitamin A deficient rats the fetus develops a high incidence of defects of the aortopulmonary septum (44%), the ventricular septum, and the aortic arches.[51] Two fetuses were noted to have anomalous origin of the RPA from the ascending aorta. In this 1950 report, the authors speculated that such an anomaly might possibly occur in humans, a prediction that was verified in subsequent case reports. Several workers have noted highly specific cardiovascular teratologic effects when Fertilysin, an oral abortifacient, is administered to rodents. Abnormal origin of the pulmonary artery from distinct aortic and pulmonic trunks was noted in 17 to 163 hamster fetuses examined on the 15th day of gestation after Fertilysin administration on the 8th and 9th days.[52]

Quail-chick chimera experiments have demonstrated that the tunica media and adventitia, but not the endothelium, of the large branchial arch arteries originate from mesoectodermal cells derived from the neural crest.[53] These mesoectodermal cells extend into the arterial outflow portion of the heart and participate in aortopulmonary and conotruncal septation.[53,54] Selective ablation of premigratory neural crest tissue from somites 1 through 5 in chick embryos results in a significant incidence of persistent truncus arteriosus, VSD, and double outlet right ventricle.[55] Previous workers[56] also have demonstrated the importance of a population of extracardiac cells that migrate into the aortopulmonary septum. Recent work strongly suggests that these cells are derived from the neural crest.[54,55] Use of these techniques may prove to specifically identify the developmental abnormalities responsible for the lesion of discussion.

Recent studies on the genetic and hemodynamic aspects of congenital cardiovascular lesions suggest that specific lesions involving the conotruncal portion of the heart frequently coexist with other conotruncal defects[57,58] and that aortic arch anomalies are frequently associated with VSDs.[59] Although coexisting cardiac and extracardiac defects may be produced by alterations in the embryonic hemodynamic factors,[60] the relative importance of genetic and hemodynamic factors in the pathogenesis of specific lesions remains unknown.

Discussion

Patients with origin of the RPA from the ascending aorta usually present during infancy with respiratory distress, failure to thrive, tachycardia, and a heart murmur. Cyanosis occurs in nearly half of these patients. Experimental studies have shown no change in resting arterial saturation unless 85% of the lung is removed. When a pulmonary artery is ligated, oxygen uptake simply doubles on the contralateral side, maintaining adequate oxygenation. The lung on the occluded side decreases its ventilation by bronchoconstriction as a con-

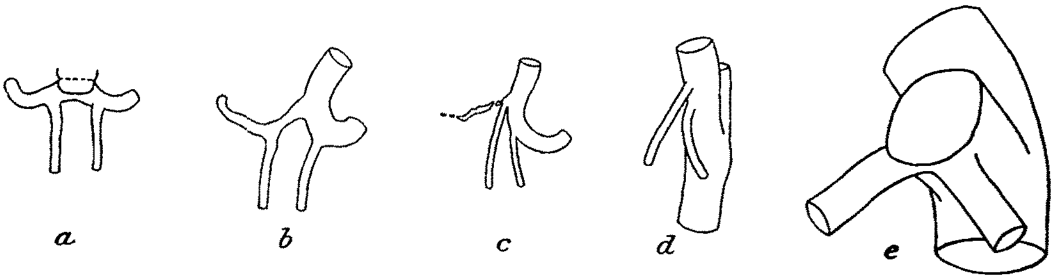

FIG. 7. Development of the pulmonary arteries (Congdon, 1922).

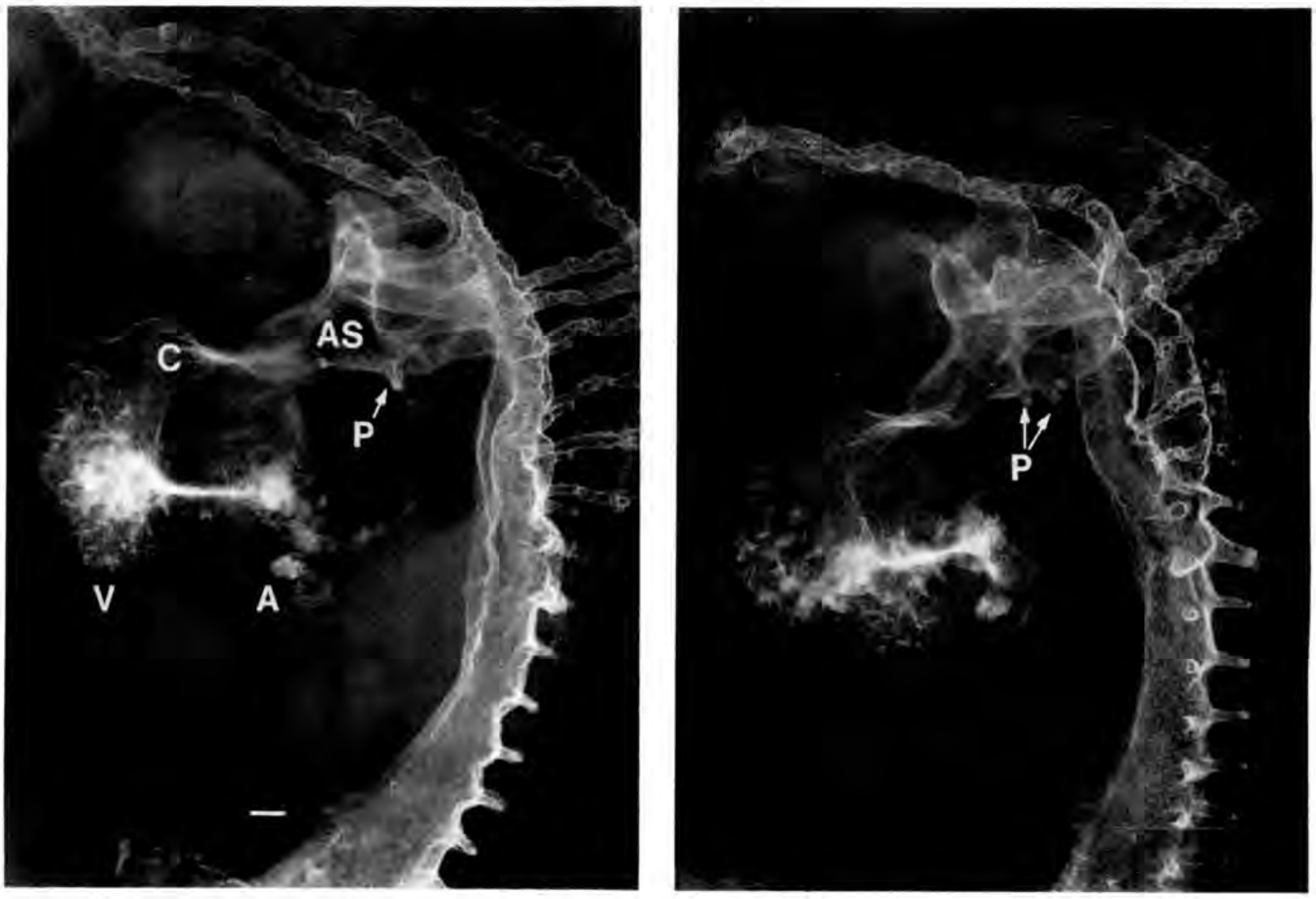

FIG. 8. *Left.* Lateral microradiograph of a mouse embryo at 11.5 days of gestation (6.5 mm crown rump length). *Right.* Left anterior oblique microradiograph of the same. Embryos were prepared and studied by perfusion-fixation with glutaraldehyde through the umbilical vein, retrograde injection of the umbilical artery with 5% silver nitrate, critical point drying, and radiography on high-resolution plates. The method renders the endothelial surface opaque. The line at the bottom equals 0.1 mm (100 μm). These two views demonstrate the close origin of the right and left pulmonary arteries (P) to the posterior aspect of the aortic sac (AS). The conotruncal portion of the arterial outflow (C) is undergoing division. Atria (A) and ventricles (V) connected by narrow atrioventricular canal formed by superior and inferior endocardial cushions.

sequence of alveolar hypocapnea. This explains the reason arterial saturation is normal in these patients unless gas exchange is impaired by pulmonary edema, bronchopneumonia, or right-to-left shunting through an associated anomaly.

Chest films uniformly reveal cardiomegaly, and increased pulmonary vascularity, either bilaterally or on the right side only, is present in all patients and is not influenced by associated anomalies. EKGs are nonspecific with right-sided, left-sided, and biventricular hypertrophy being present and are independent of concomitant lesions. Therefore, a specific diagnosis cannot be made based solely on the history, physical examination, chest film, and EKG.

Other noninvasive techniques have been more successful in establishing a diagnosis of this anomaly as well as associated defects. Suprasternal notch two-dimensional echocardiography is helpful in evaluating the ascending aorta and pulmonary arteries.[30,61-63] Other windows may identify most defects associated with aortic origin of the RPA except for PDA. Using conventional two-dimensional echocardiography, PDA, in general, is not visualized unless it is large, *e.g.*, when there is systemic dependence on its patency.[30] Newer techniques, including standard doppler methods and color-flow doppler, have improved the sensitivity of echocardiography. Magnetic resonance imaging is an excellent noninvasive method for depicting congenital abnormalities of the heart and great vessels, and may provide otherwise unobtainable information.[64] Radionuclide angiography has also been performed in the diagnosis of anomalous origin of the RPA from the ascending aorta.[40]

Experimental studies by Levy and Blalock revealed that pulmonary hypertension did not develop after anastomosis of the left subclavian artery to the LPA.[65] However, Muller et al. were able to induce pulmonary hypertension after anastomosis of the descending aorta to the LPA; at 1 year the degree of hypertension was proportional to the size of the anastomosis.[66] Dammann et al. produced lobar pulmonary hypertension by connecting the LPA to the left upper lobe branch of the pulmonary artery with subsequent development of intimal hyperplasia and medial hypertrophy.[67] Based on these studies, it is believed that the most important determinants of the severity of pulmonary hypertension are size of anastomosis (or connection) and size of the pulmonary vascular bed.

It is interesting to speculate on why pulmonary hypertension occurs on the left side. After a pneumonectomy, 100% of the right ventricular output flows to one lung, yet little increase in pulmonary pressure has been noted up to 11 years.[68,69] In fact, both experimental and clinical studies have indicated that up to 75% reduction in lung volumes does not produce pulmonary hypertension.[70–73] Acute and chronic ligation of a pulmonary artery has also been done in both animals and humans without producing elevated pulmonary pressures.[74–76] Rudolf et al. reported the long-term effects of pneumonectomy or ligation of one pulmonary artery in adult dogs compared with 1- to 2-month-old puppies,[77] and noted moderate progressive increases in pulmonary pressure, which, in a number of animals, showed a tendency towards return to normal. There were greater pressure increases in the puppies, but significant pulmonary hypertension did not develop. In fetal studies, ligation of the ductus arteriosus led to pulmonary hypertension for at least 24 hours.[78] Unilateral ligation of a pulmonary artery caused varying degrees of moderate pulmonary hypertension; however, the study did not continue to postpartem when inflation of the lung results in reduced pulmonary vascular resistance.[79]

The cause of elevated LPA pressure in patients with aortic origin of the RPA is not known. It is postulated that there is a reflex vasoconstriction, or "neurogenic crossover."[30,73] The study of Rudolf et al. of ligation or pneumonectomy was performed in 1–2-month-old puppies. By 8 weeks an "adult"-type pulmonary vasculature has replaced the "fetal" characteristics, defined by lumen-to-wall ratios.[80] It is possible that increased flow may cause pulmonary hypertension when fetal vasculature is present. It is not known whether ligation or pneumonectomy in the neonate produces significant pulmonary hypertension in the contralateral lung. An experimental model that reproduces aortic origin of the RPA and its pathophysiology has not been performed. Irreversible changes of pulmonary hypertension develop on the left side even in patients without left-to-right shunts.

Clearly, anatomic repair of aortic origin of the RPA has led to substantial improvement in survival. The selection of a primary repair *versus* synthetic graft interposition has not affected operative mortality or 1-year survival. Long-term patency of the RPA after either repair is not documented. In fact, before this report, the latest follow-up evaluating pulmonary flow was at 4 years. Our patient required operative intervention because of failure to thrive. He returned to normal growth and is now asymptomatic at 10 years after operation.

The long-term effect of unilateral pulmonary artery occlusion is not known. A related situation may be the congenital malformation of pulmonary artery sling. The currently advocated surgical repair of this lesion is division of the anomalous vessel and primary anastomosis of the proximal LPA to the MPA. Such patients have been studied as long as 24 years after operation.[81] Most survivors remain asymptomatic with no flow through the LPA. Mechanisms of the obstruction to pulmonary blood flow in pulmonary artery sling are believed to be variable with thrombosis and cicatrical stenosis as the most likely causes.[82] Improved patency results have been reported recently and are attributed to advances in microsurgical techniques of primary anastomosis.[83] Attempts to reconstruct the occluded vessels have failed in the past.

Both histopathologic pulmonary vascular changes and physiologic responses to operation are related to the patient's age. All patients in whom pulmonary histology was examined during their first month of life, before surgery, had no pathologic changes. Medial hypertrophy and intimal hyperplasia occur in the setting of increased pulmonary blood flow and are generally considered reversible. Intimal hyperplasia, however, progresses to intimal fibrosis with continued insult. The current review shows simultaneous onset of both medial hypertrophy and intimal hyperplasia as early as 1 month of age. Intimal fibrosis has been seen as early as 1–2 months. All those in whom correction was performed within 1 month of life normalized their pulmonary artery pressures after operation. Non-normalization of pulmonary pressures after correction has occurred in patients as young as 4 months and increases in proportion to patient age. It is interesting that non-normalization of pressures occurred in patients considered to have reversible histopathologic changes. This may be related to an inadequate follow-up to allow full regression of these changes. Theoretically, associated anomalies that increase pulmonary blood flow should accelerate the process of histopathologic changes. However, no statistical correlation was evident in this review.

The developmental error responsible for anomalous origin of the RPA is unclear. With the high incidence of aortopulmonary septal abnormalities associated with this lesion, the malseptation hypothesis is attractive. Teratogenic studies, which have produced arch defects, may prove useful in differentiating among the various hypotheses in the future.

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Book Reviews

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Tumor Markers and Tumor-Associated Antigens. Bimal C. Ghosh, Luna Ghosh. 343 pp. New York: McGraw-Hill Book Co. 1987. $59.50.

THIS BOOK PROVIDES current information about tumor markers and is directed toward students and professionals engaged in cancer research and treatment. Drs. Bimal and Luna Ghosh have co-edited a good reference text on the subject that will be of value to those interested in the field. The book describes the current state of knowledge involving the characterization of tumor markers and tumor-associated antigens for all aspects of human cancer. It also describes the use of various reagents to detect these markers in cancer patients and their clinical significance in diagnosis, prognosis, and treatment. Some of the best chapters include those describing the use of carcinoembryonic antigen (58 references), tumor markers in pancreatic tumors (97 references), breast cancer (61 references), melanoma (63 references), soft tissue sarcomas (58 references), endocrine tumors (112 references), lymphomas and leukemias (99 references), and the use of the monoclonal antibodies in immunopathology (124 references). The last chapter also includes a useful appendix describing the immunoperoxidase technique, which is an important tool for detecting tumor markers and tumor-associated antigens in tissue sections. The book is well organized, easy to follow, and contains a comprehensive reference list at the conclusion of each chapter. The only limitation of such a book is the rapid pace of this scientific field and the burgeoning number of markers and antigens that are described in the literature each month. Nevertheless, this book provides a good baseline describing current knowledge in this field and should be useful to anyone who is interested in this important area of scientific and clinical investigation.

CHARLES M. BALCH, M.D.
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Anesthesia and Uncommon Pediatric Diseases. Jordan Katz, David J. Steward. 560 pp. Philadelphia: W.B. Saunders Co. 1987. $65.00.

THIS TEXT is a comprehensive review of many common and uncommon diseases of infancy and childhood that have an impact on anesthetic and surgical practice. In this book Drs. Katz and Steward, together with 21 contributing authors, all recognized experts in the field of pediatric anesthesia, provide the scientific basis and the clinical knowledge requisite for the medical and anesthetic management of each disease.

In general, the text is well organized, reviewing all aspects of childhood illnesses to be encountered in the perioperative period. The distinctive hallmark of this text is the integration of pathophysiologic principles with clinical experience and practice. The book begins with chapters on anatomy, physiology, and pharmacology with specific reference to the special differences in children when compared with adults. The second section of the text deals with disease states of the major organ systems. It includes detailed discussion of the various childhood diseases of the central nervous system, respiratory system, cardiovascular system, renal system, and gastrointestinal system. The remainder of the text reviews childhood diseases as they relate to anatomic approaches, *e.g.,* head and neck syndromes, opthalmologic, otolaryngologic, or systemic diseases (hematologic, metabolic, and infectious illnesses). Within each chapter the pathophysiology is discussed in detail as well as the surgical procedure and anesthetic implications.

The weaknesses of the book are that some chapters are too wordy and lengthy. A second minor criticism is that most of the material can be found in other texts, albeit not as consolidated as this text. This book is not for the generalist. It contains highly specialized material as it relates to diseases of children and it is aimed at the instruction of physicians who deal intensively with the pediatric patient. This text is especially recommended for those physicians whose clinical practice of medicine depends heavily on the knowledge of childhood disease states, operative procedures, and subsequent anesthetic management.

In the preface Drs. Katz and Steward state "We have attempted to assemble more than a simple book of anesthesia-related facts and have designed this volume to provide a detailed summary backed by knowledge which related to each disease." I believe this text admirably accomplishes this intention. Surgeons, anesthesiologists, and intensive care providers involved in the care of children will find this text an invaluable resource and the supplement of major texts.

WILLIAM J. GREELEY, M.D.
Durham, North Carolina

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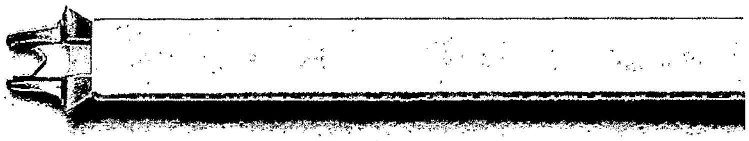

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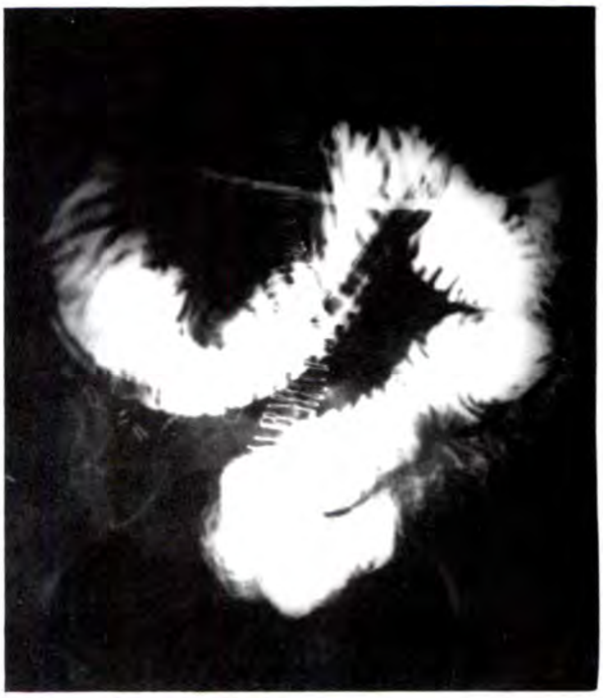
CASE # 24 **AGE:** 55 **SEX:** FEMALE
DIAGNOSIS: CECAL CARCINOMA
SYMPTOMS: ANEMIA (Hg 6 gm/dl)
OPERATION: RIGHT HEMICOLECTOMY & GASTROSTOMY

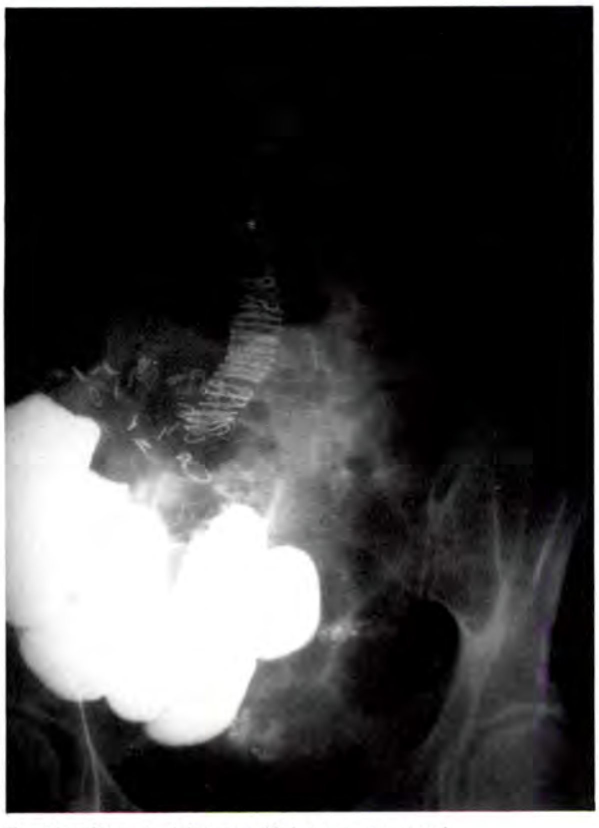
The patient had a right hemicolectomy with stapled (U.S. Surgical Corp) anastomosis and fascia closure and a MOSS® gastrostomy tube. The stomach and proximal duodenum were aspirated, with immediate simultaneous feeding into the distal duodenum.

Barium feeding 5 hours postop documented adequate motility. The deliberate excess was totally removed. No contrast (i.e.: excess feeding) escaped efficient aspiration within the proximal duodenum, to reflux into the stomach. (Figure A) Serial motility study showed barium had traversed the anastomosis and colon, and already was exiting in a spontaneous bowel movement by 21 hours postop. (Figure C)

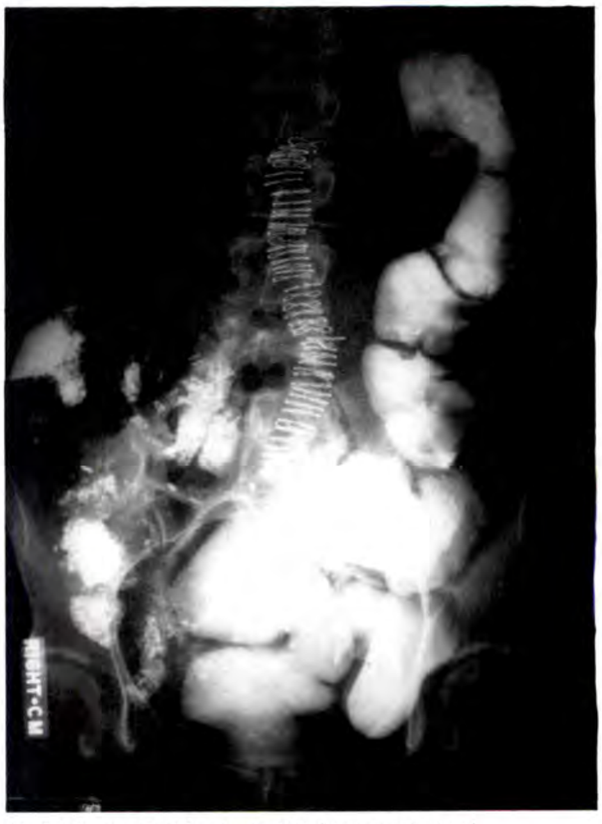
She received 300 ml/hr of Vivonex TEN (Norwich Eaton Pharm), absorbed 5,000 kcal the initial 20 hours, and then tolerated a general diet. She was the 4th patient discharged uneventfully 24 hours after bowel resection and reanastomosis.



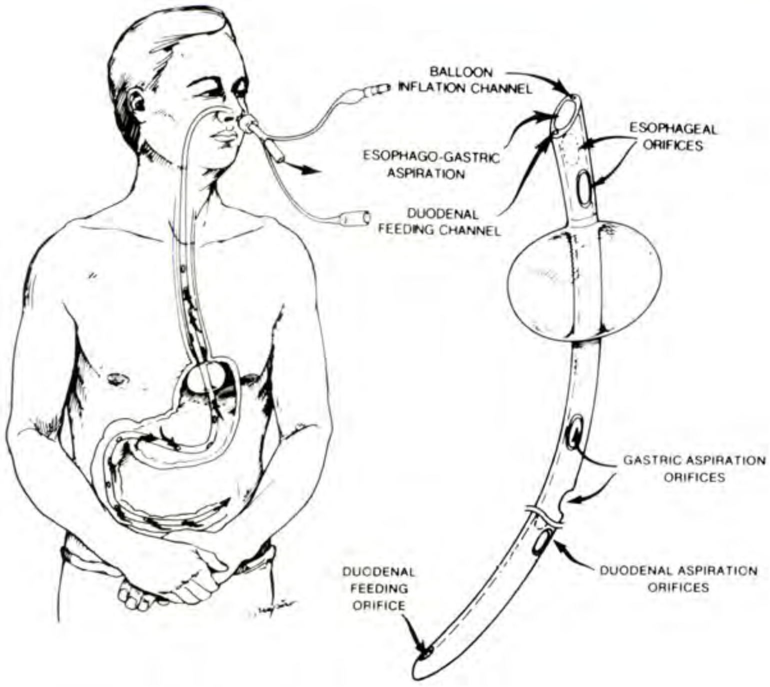
A. Study @ 5 minutes (5 hours postop).
Note efficient removal of all excess barium, with none reaching the stomach.



B. Motility @ 4 hours (9 hours postop).
All barium is within the ileum.



C. Motility @ 16 hours (21 hours postop).
Barium is exiting in a spontaneous bowel movement.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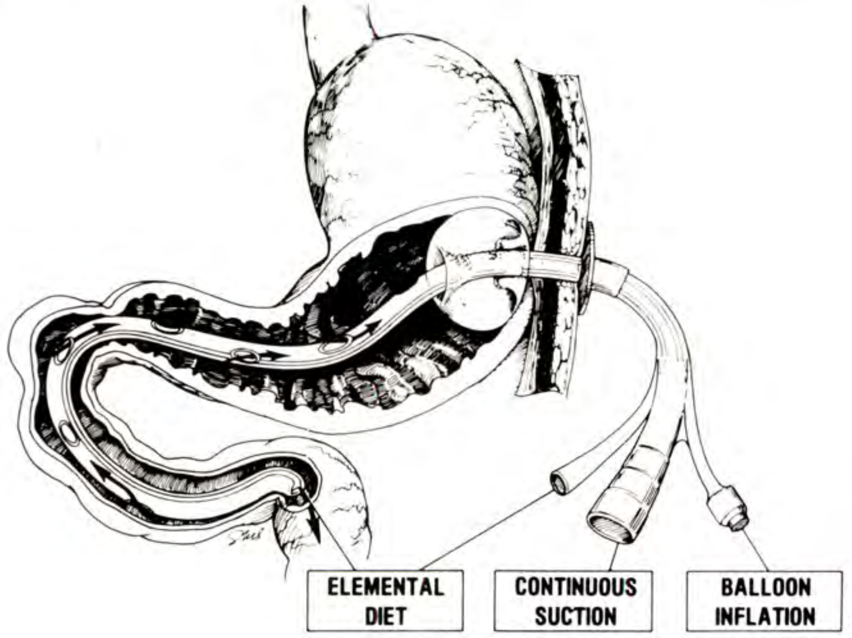

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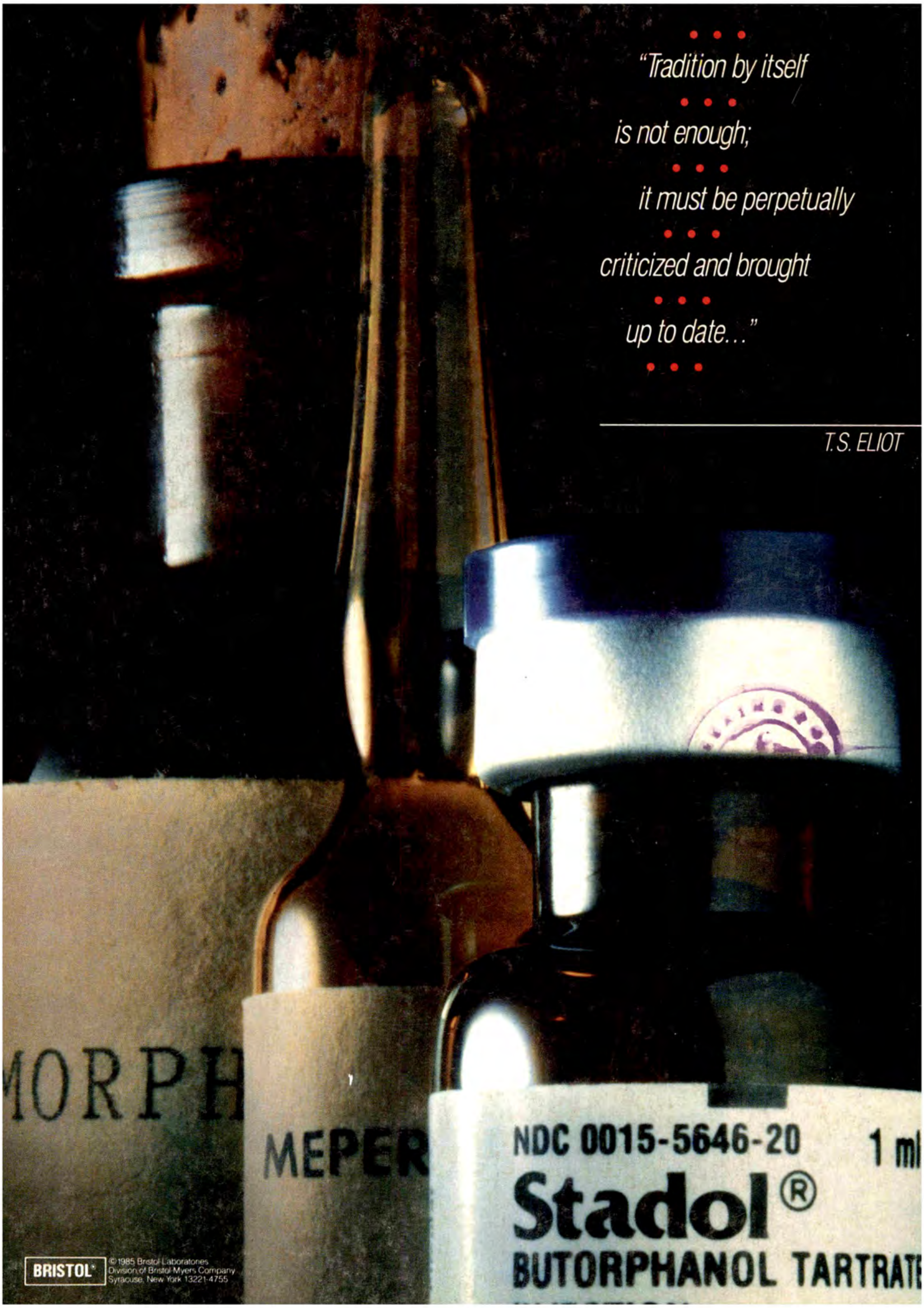

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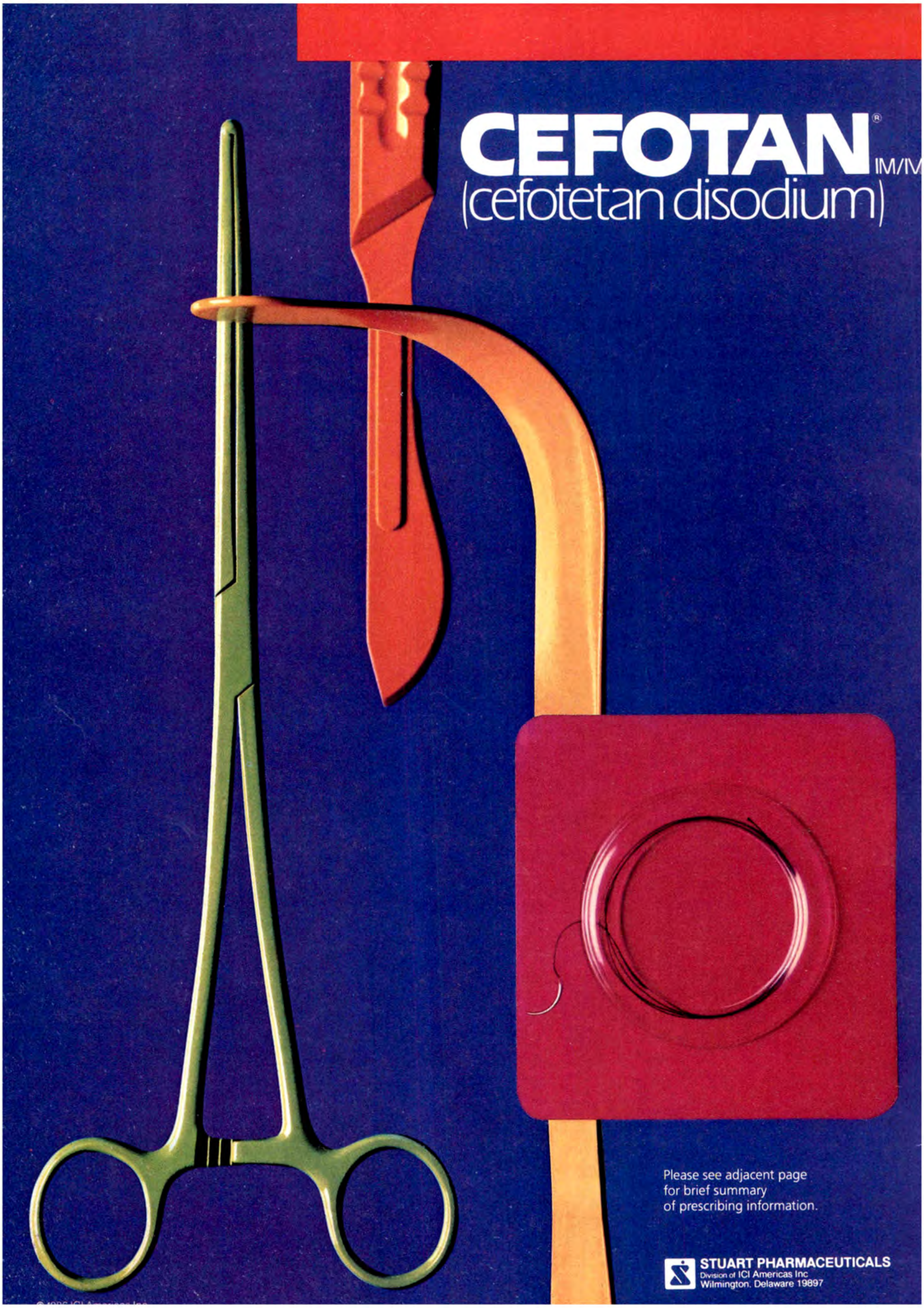

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BRIEF SUMMARY

INDICATIONS AND USAGE
TREATMENT: CEFOTAN® (cefotetan disodium) is indicated for the therapeutic treatment of the following infections when caused by susceptible strains of the designated organisms:

Urinary tract infections caused by *E coli*, *Klebsiella* species (including *K pneumoniae*), *Proteus mirabilis* and *Proteus* sp (which may include the organisms now called *Proteus vulgaris*, *Providencia rettgeri*, and *Morganella morganii*).

Lower respiratory tract infections caused by *Streptococcus pneumoniae* (formerly *D pneumoniae*), *Staphylococcus aureus* (penicillinase- and nonpenicillinase-producing strains), *Haemophilus influenzae* (including ampicillin-resistant strains), *Klebsiella* species (including *K pneumoniae*), and *E coli*.

Skin and skin structure infections caused by *Staphylococcus aureus* (penicillinase- and nonpenicillinase-producing strains), *Staphylococcus epidermidis*,* *Streptococcus pyogenes* and *Streptococcus* species (excluding enterococci), and *E coli*.

Gynecologic infections caused by *Staphylococcus aureus*† (including penicillinase- and nonpenicillinase-producing strains), *Staphylococcus epidermidis*,* *Streptococcus* species (excluding enterococci), *E coli*, *Proteus mirabilis*, *Neisseria gonorrhoeae*, *Bacteroides* species (excluding *B distasonis*, *B ovatus*, *B thetaiotaomicron*), *Fusobacterium* species,† and gram-positive anaerobic cocci (including *Peptococcus* and *Peptostreptococcus* species†).

Intra-abdominal infections caused by *E coli*, *Klebsiella* species (including *K pneumoniae*†), *Streptococcus* species (excluding enterococci), and *Bacteroides* species (excluding *B distasonis*, *B ovatus*, *B thetaiotaomicron*).

Bone and joint infections caused by *Staphylococcus aureus*.†

***NOTE:** Some strains of *Staphylococcus epidermidis* are resistant to cefotetan.

†Efficacy for this organism in this organ system was studied in fewer than ten infections.

PROPHYLAXIS: The preoperative administration of CEFOTAN may reduce the incidence of certain postoperative infections in patients undergoing surgical procedures that are classified as clean contaminated or potentially contaminated (eg, cesarean section, abdominal or vaginal hysterectomy, transurethral surgery, biliary tract surgery, and gastrointestinal surgery).

The prophylactic dose of CEFOTAN should be administered 30 to 60 minutes prior to surgery. In patients undergoing cesarean section, CEFOTAN should be administered intravenously after the clamping of the umbilical cord.

If there are signs and symptoms of infection, specimens for culture should be obtained for identification of the causative organism so that appropriate therapeutic measures may be initiated.

CONTRAINDICATIONS
CEFOTAN is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

WARNINGS
Before therapy with CEFOTAN is instituted, careful inquiry should be made to determine whether the patient has had previous hypersensitivity reactions to cefotetan disodium, cephalosporins, penicillins, or other drugs. This product should be given cautiously to penicillin-sensitive patients. Antibiotics should be administered with caution to any patient who has demonstrated some form of allergy, particularly to drugs. If an allergic reaction to CEFOTAN occurs, discontinue the drug. Serious acute hypersensitivity reactions may require epinephrine and other emergency measures.

Pseudomembranous colitis has been reported with the use of cephalosporins (and other broad-spectrum antibiotics); therefore, it is important to consider its diagnosis in patients who develop diarrhea in association with antibiotic use.

Treatment with broad-spectrum antibiotics may alter normal flora of the colon and may permit overgrowth of clostridia. Studies indicate a toxin produced by *Clostridium difficile* is one primary cause of antibiotic-associated colitis. Cholestyramine and colestipol resins have been shown to bind the toxin in vitro.

Mild cases of colitis may respond to drug discontinuance alone. Moderate to severe cases should be managed with fluid, electrolyte, and protein supplementation as indicated. When the colitis is not relieved by drug discontinuance, or when it is severe, oral vancomycin is the treatment of choice for antibiotic-associated pseudomembranous colitis produced by *C difficile*. Other causes should also be considered.

PRECAUTIONS
GENERAL: As with other broad-spectrum antibiotics, prolonged use of CEFOTAN may result in overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection does occur during therapy, appropriate measures should be taken.

In common with many other broad-spectrum antibiotics, CEFOTAN may be associated with a fall in prothrombin activity. Those at risk include patients with renal or hepatic impairment, or poor nutritional state. Prothrombin times should be monitored in patients at risk and exogenous Vitamin K administered as indicated.

CEFOTAN should be used with caution in individuals with a history of gastrointestinal disease, particularly colitis.

INFORMATION FOR PATIENTS: As with some other cephalosporins, a disulfiram-like reaction characterized by flushing, sweating, headache, and tachycardia may occur when alcohol (beer, wine, etc) is ingested within 72 hours after CEFOTAN administration. Patients should be cautioned about the ingestion of alcoholic beverages following the administration of CEFOTAN.

DRUG INTERACTIONS: If CEFOTAN and an aminoglycoside are used concomitantly, renal function should be carefully monitored, especially if higher dosages of the aminoglycoside are to be administered or if therapy is prolonged, because of the potential nephrotoxicity and ototoxicity of aminoglycoside antibiotics. Although, to date, nephrotoxicity has not been noted when CEFOTAN was given alone, it is possible that nephrotoxicity may be potentiated if CEFOTAN is used concomitantly with an aminoglycoside.

DRUG/LABORATORY TEST INTERACTIONS: A false positive reaction for glucose in urine may occur with Benedict's or Fehling's solution.

As with other cephalosporins, high concentrations of cefotetan may interfere with measurement of serum and urine creatinine levels of Jaffe reaction and produce false increases in the levels of creatinine reported.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY: Although long-term studies in animals have not been performed to evaluate carcinogenic potential, no mutagenic potential of cefotetan was found in standard laboratory tests.

Cefotetan has adverse effects on the testes of prepubertal rats. Subcutaneous administration of 500 mg/kg/day (approx 8-16 times the usual adult human dose) on days 6-35 of life (thought to be

CEFOTAN® (cefotetan disodium)

developmentally analogous to late childhood and prepuberty in humans) resulted in reduced testicular weight and seminiferous tubule degeneration in 10 of 10 animals. Affected cells included spermatogonia and spermatocytes; Sertoli and Leydig cells were unaffected. Incidence and severity of lesions were dose-dependent; at 120 mg/kg/day (approx 2-4 times the usual human dose), only 1 of 10 treated animals was affected, and the degree of degeneration was mild. Similar lesions have been observed in experiments of comparable design with other methylthiotetrazole-containing antibiotics and impaired fertility has been reported, particularly at high dose levels. No testicular effects were observed in 7-week-old rats treated with up to 1000 mg/kg/day SC for 5 weeks, or in infant dogs (3 weeks old) that received up to 300 mg/kg/day IV for 5 weeks. The relevance of these findings to humans is unknown.

USAGE IN PREGNANCY: Pregnancy Category B: Reproduction studies have been performed in rats and monkeys at doses up to 20 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to cefotetan. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

USAGE IN NURSING MOTHERS: Cefotetan is excreted in human milk in very low concentrations. Caution should be exercised when cefotetan is administered to a nursing woman.

PEDIATRIC USE: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS
In clinical studies the following adverse effects were considered related to CEFOTAN therapy.

Gastrointestinal symptoms occurred in 1.5 percent of patients; the most frequent were diarrhea (1 in 80) and nausea (1 in 700).

Hematologic laboratory abnormalities occurred in 1.4 percent of patients and included eosinophilia (1 in 200), positive direct Coombs' test (1 in 250), and thrombocytosis (1 in 300).

Hepatic enzyme elevations occurred in 1.2 percent of patients and included a rise in SGPT (1 in 150), SGOT (1 in 300), alkaline phosphatase (1 in 700), and LDH (1 in 700).

Hypersensitivity reactions were reported in 1.2 percent of patients and included rash (1 in 150) and itching (1 in 700).

Local effects were reported in less than one percent of patients and included phlebitis at the site of injection (1 in 300), and discomfort (1 in 500).

DOSAGE AND ADMINISTRATION
TREATMENT: The usual adult dosage is 1 or 2 grams of CEFOTAN administered intravenously or intramuscularly every 12 hours for 5 to 10 days. Proper dosage and route of administration should be determined by the condition of the patient, severity of the infection, and susceptibility of the causative organism.

GENERAL GUIDELINES FOR DOSAGE OF CEFOTAN

Type of Infection	Daily Dose	Frequency and Route
Urinary Tract	1-4 grams	500 mg every 12 hours IV or IM 1 or 2 g every 24 hours IV or IM 1 or 2 g every 12 hours IV or IM
Other Sites	2-4 grams	1 or 2 g every 12 hours IV or IM
Severe	4 grams	2 g every 12 hours IV
Life-Threatening	6* grams	3 g every 12 hours IV

*Maximum daily dosage should not exceed 6 grams.

PROPHYLAXIS: To prevent postoperative infection in clean contaminated or potentially contaminated surgery in adults, the recommended dosage is 1 or 2 g of CEFOTAN administered once, intravenously, 30 to 60 minutes prior to surgery. In patients undergoing cesarean section, the dose should be administered as soon as the umbilical cord is clamped.

IMPAIRED RENAL FUNCTION: When renal function is impaired, a reduced dosage schedule must be employed. The following dosage guidelines may be used.

DOSAGE GUIDELINES FOR PATIENTS WITH IMPAIRED RENAL FUNCTION

Creatinine Clearance mL/min	Dose	Frequency
>30	Usual Recommended Dose*	Every 12 hours
10-30	Usual Recommended Dose*	Every 24 hours
<10	Usual Recommended Dose*	Every 48 hours

*Dose determined by the type and severity of infection, and susceptibility of the causative organism.

Cefotetan is dialyzable and it is recommended that for patients undergoing intermittent hemodialysis, one-quarter of the usual recommended dose be given every 24 hours on days between dialysis and one-half the usual recommended dose on the day of dialysis.

HOW SUPPLIED
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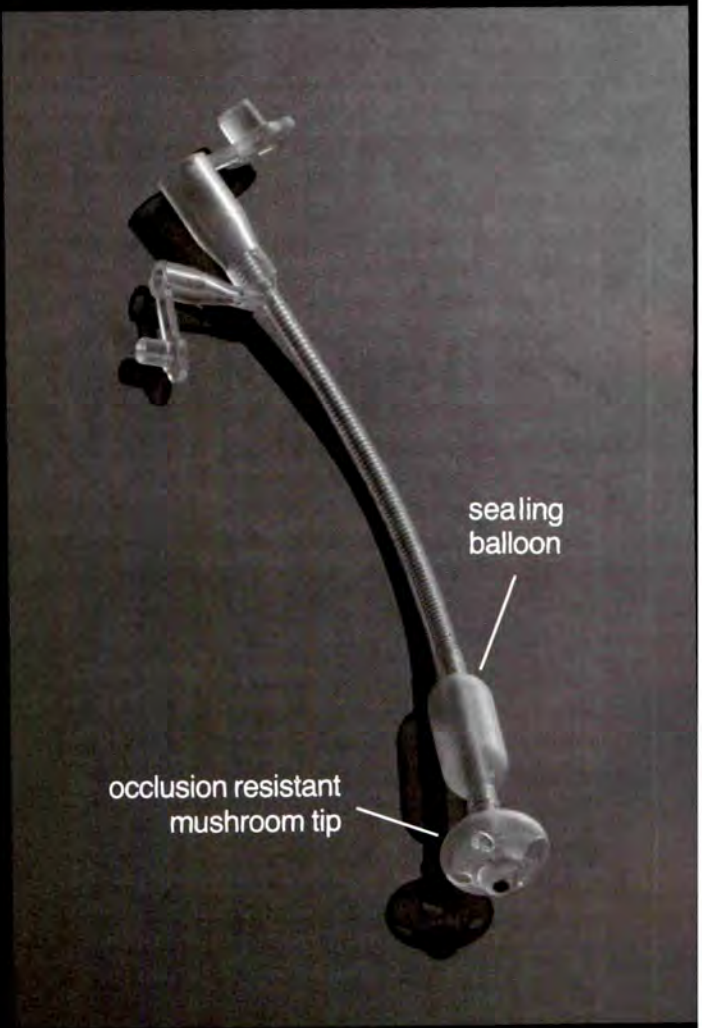

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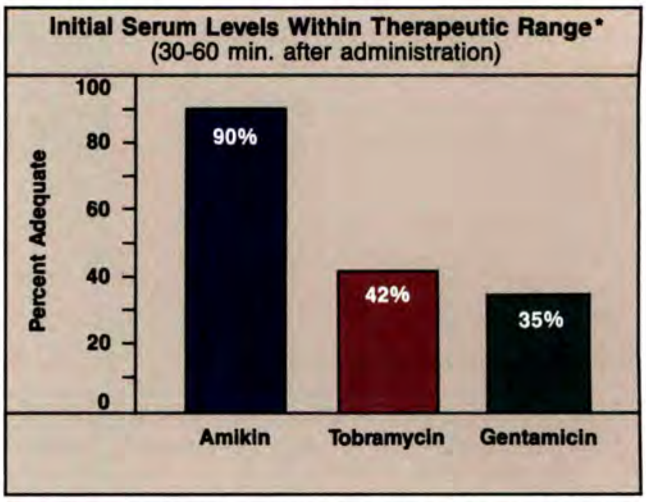

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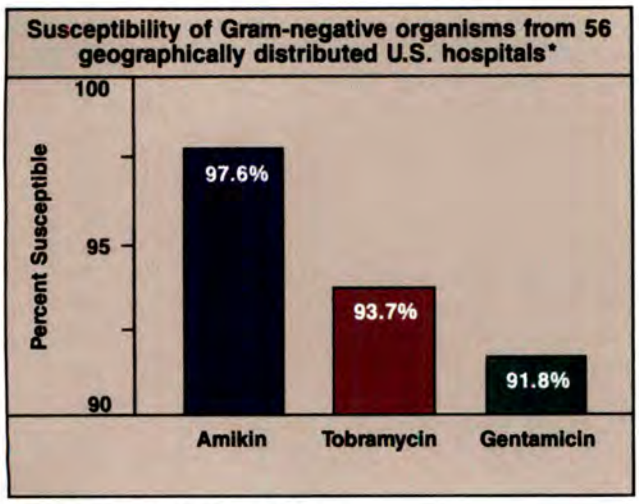

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WARNINGS

Patients treated with aminoglycosides should be under close clinical observation because of the potential ototoxicity and nephrotoxicity associated with their use.

Ototoxicity, both auditory and vestibular, can occur in patients treated at higher doses or for periods longer than those recommended. The risk of amikacin-induced ototoxicity is greater in patients with renal damage. High frequency deafness usually occurs first and can be detected only by audiometric testing. Vertigo may occur and may be evidence of vestibular injury.

The ototoxicity potential of amikacin in infants is not known. Until more safety reports become available, amikacin should be used in infants only in those specific circumstances when susceptibility testing indicates that other aminoglycosides cannot be used or are otherwise contraindicated, and when the infant can be observed closely for evidence of toxicity.

Aminoglycosides are potentially nephrotoxic. Renal and eighth-nerve function should be closely monitored in patients with known or suspected renal impairment and also in those whose renal function is initially normal but who develop signs of renal dysfunction during therapy. Such impairment may be characterized by decreased creatinine clearance, the presence of cells or casts, oliguria, proteinuria, decreased urine specific gravity or evidence of increasing nitrogen retention (increasing BUN or creatinine).

Evidence of impairment in renal, vestibular or auditory function requires discontinuation of the drug or dosage adjustment.

Serum concentrations should be monitored when feasible, and prolonged peak concentrations above 35 mcg/ml should be avoided. Urine should be examined for increased excretion of protein, the presence of cells and casts, and decreased specific gravity.

Concurrent and/or sequential use of topically or systemically neurotoxic or nephrotoxic antibiotics, particularly kanamycin, gentamicin, tobramycin, neomycin, streptomycin, cephaloridine, paromomycin, viomycin, polymyxin B, colistin and vancomycin should be avoided.

AMIKIN should not be given concurrently with potent diuretics (ethacrynic acid, furosemide, meralluride sodium, sodium mercaptomerin or mannitol). Some diuretics themselves cause ototoxicity, and intravenously administered diuretics enhance aminoglycoside toxicity by altering antibiotic concentrations in serum and tissue.

CONTRAINDICATIONS

A history of hypersensitivity to amikacin is a contraindication for its use.

WARNINGS

See "Warning" box above.

PRECAUTIONS

AMIKIN is potentially nephrotoxic, ototoxic, and neurotoxic. The concurrent or serial use of other ototoxic or nephrotoxic agents should be avoided either systemically or topically because of the potential for additive effects. Such agents include antibacterial drugs such as kanamycin, gentamicin, tobramycin, neomycin, streptomycin, cephaloridine, paromomycin, viomycin, polymyxin B, colistin and vancomycin as well as certain diuretic agents such as ethacrynic acid or furosemide.

Ototoxicity — See "Warning" box.

Nephrotoxicity — Since AMIKIN is present in high concentrations in the renal excretory system, patients should be well hydrated to minimize chemical irritation of the renal tubules. Kidney function should be assessed by the usual methods prior to starting therapy and daily during the course of treatment.

If signs of renal irritation appear (casts, white or red cells or albumin), hydration should be increased. A reduction in dosage (see "Dosage and Administration") may be desirable if other evidence of renal dysfunction occurs such as decreased creatinine clearance, decreased urine specific gravity, increased BUN, creatinine or oliguria. If azotemia increases or if a progressive decrease in urinary output occurs, treatment should be stopped.

Note: When patients are well hydrated and kidney function is normal the risk of nephrotoxic reactions with amikacin is low if the dosage recommendations (see "Dosage and Administration") are not exceeded.

Neurotoxicity — Neuromuscular blockade and muscular paralysis have been demonstrated in the cat with high doses of amikacin (188 mg/Kg). The possibility of neuromuscular blockade and respiratory paralysis should be considered when amikacin is administered concomitantly with anesthetic or neuromuscular blocking drugs. If blockade occurs, calcium salts may reverse this phenomenon.

Other — Cross-allergenicity among aminoglycosides has been demonstrated. As with other antibiotics the use of amikacin may result in overgrowth of nonsusceptible organisms. If this occurs, appropriate therapy should be instituted.

Pregnancy — Reproduction studies have been performed in rats and mice and have revealed no evidence of impaired fertility or harm to the fetus due to amikacin. There are no well-controlled studies in pregnant women but investigational experience does not include any positive evidence of adverse effects on the fetus. Although there is no clearly defined risk, such experience cannot exclude the possibility of infrequent or subtle damage to the fetus. AMIKIN should be used in pregnant women only when clearly needed.

It is not known whether this drug is excreted in human milk. As a general rule, nursing should not be undertaken while a patient is on a drug since many drugs are excreted in human milk.

ADVERSE REACTIONS

Ototoxicity — See "Warning" box.

Nephrotoxicity — Albuminuria, presence of red and white cells, casts, azotemia and oliguria have been reported.

Other — In addition to those described above, other adverse reactions which have been reported on rare occasions are skin rash, drug fever, headache, paresthesia, tremor, nausea and vomiting, eosinophilia, arthralgia, anemia, hypotension.

Overdosage — In the event of overdosage or toxic reaction, peritoneal dialysis or hemodialysis will aid in the removal of amikacin from the blood.

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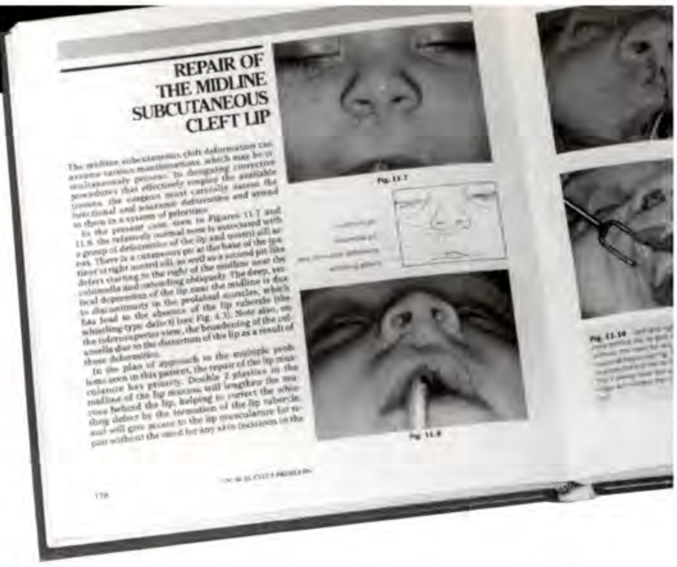

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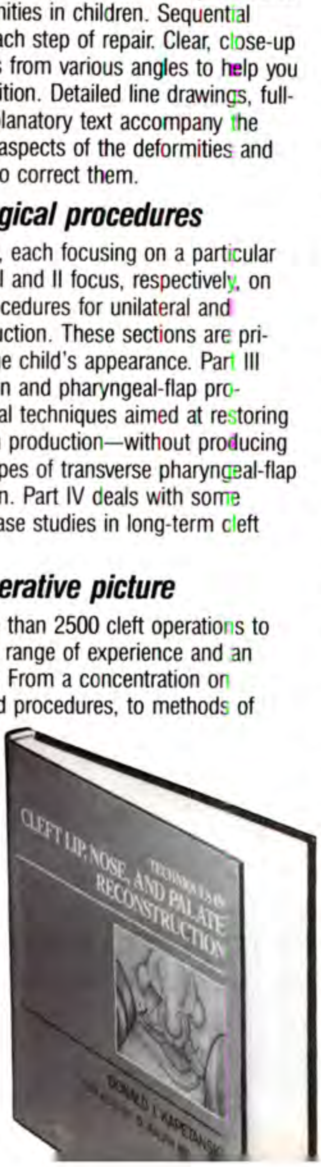

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NOLVADEX is effective in delaying recurrence following total mastectomy and axillary dissection in postmenopausal women with breast cancer (T1-3, N1, M0). The estrogen and progesterone receptor values may help to predict whether NOLVADEX therapy is likely to be beneficial. In some NOLVADEX adjuvant studies, most of the benefit to date has been in the subgroup with 4 or more positive axillary nodes.

CONTRAINDICATIONS: None known.

WARNINGS: Pregnancy Category D: NOLVADEX may cause fetal harm when administered to a pregnant woman. Individuals should not become pregnant while taking NOLVADEX. Effects on reproductive functions are expected from the antiestrogenic properties of the drug. In reproductive studies in rats at dose levels equal to or below the human dose, nonteratogenic developmental skeletal changes were seen and were found to be reversible. In addition, in fertility studies in rats and in teratology studies in rabbits using doses at or below those used in humans, a lower incidence of embryo implantation and a higher incidence of fetal death or retarded in utero growth were observed, with slower learning behavior in some rat pups. The impairment of learning behavior did not achieve statistical significance in one study, and, in another study where significance was reported, this was by comparing dosed animals with controls of another study. Several pregnant marmosets were dosed during organogenesis or in the last half of pregnancy. No deformations were seen and although the dose was high enough to terminate pregnancy in some animals, those that did maintain pregnancy showed no evidence of teratogenic malformations. There are no adequate and well controlled studies in pregnant women. There have been reports of spontaneous abortions, birth defects, fetal deaths, and vaginal bleeding. If this drug is used during pregnancy or the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

Ocular changes have been reported in a few patients who, as part of a clinical trial, were treated for periods greater than one year with NOLVADEX at doses at least four times the highest recommended daily dose of 40 mg. The ocular changes consist of retinopathy and, in some patients, there are also corneal changes and a decrease in visual acuity.

In addition, a few cases of ocular changes including visual disturbance, corneal changes, and/or retinopathy have been reported in patients treated with NOLVADEX at recommended doses. It is uncertain if these effects are due to NOLVADEX.

As with other additive hormonal therapy (estrogens and androgens), hypercalcemia has been reported in some breast cancer patients with bone metastasis within a few weeks of starting treatment with NOLVADEX. If hypercalcemia does occur, appropriate measures should be taken and, if severe, NOLVADEX should be discontinued.

PRECAUTIONS: General: NOLVADEX should be used cautiously in patients with existing leukopenia or thrombocytopenia. Observations of leukopenia and thrombocytopenia occasionally have been made, but it is uncertain if these effects are due to NOLVADEX therapy. Transient decreases in platelet counts, usually to 50,000-100,000/cu mm, infrequently lower, have been occasionally reported in patients taking NOLVADEX for breast cancer. No hemorrhagic tendency has been recorded and the platelet counts returned to normal levels even though treatment with NOLVADEX continued.

Laboratory Tests: Periodic complete blood counts, including platelet counts, may be appropriate.

Carcinogenesis: While no conventional bioassay has been conducted, endocrine changes in immature and mature mice were investigated in a 13-month study. Granulosa cell ovarian tumors and interstitial cell testicular tumors were found in mice receiving NOLVADEX, but not in the controls.

Mutagenesis: No genotoxic potential has been found in a battery of in vivo and in vitro tests with pro- and eukaryotic test systems with drug metabolizing systems present.

Impairment of Fertility: Fertility in female rats was decreased following administration of 0.04 mg/kg for 2 weeks prior to mating through day 7 of pregnancy. There was a decreased number of implantations, and all fetuses were found dead.

Following administration to rats of 0.16 mg/kg from days 7-17 of pregnancy, there were increased numbers of fetal deaths. Administration of 0.125 mg/kg to rabbits during days 6-18 of pregnancy resulted in abortion or premature delivery. Fetal deaths occurred at higher doses. There were no teratogenic changes in either rat or rabbit segment II studies. Several pregnant marmosets were dosed with 10 mg/kg/day either during organogenesis or in the last half of pregnancy. No deformations were seen, and, although the dose was high enough to terminate pregnancy in some animals, those that did maintain pregnancy showed no evidence of teratogenic malformations. Rats given 0.16 mg/kg from day 17 of pregnancy to 1 day before weaning demonstrated increased numbers of dead pups at parturition. It was reported that some rat pups showed slower learning behavior, but this did not achieve statistical significance in one study, and in another study where significance was reported, this was by comparing dosed animals with controls of another study.

The recommended daily human dose of 20-40 mg corresponds to 0.4-0.8 mg/kg for an average 50 kg woman.

Pregnancy Category D: See WARNINGS.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from NOLVADEX, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

ADVERSE REACTIONS: The most frequent adverse reactions to NOLVADEX are hot flashes, nausea and vomiting. These may occur in up to one fourth of patients, but are rarely severe enough to require discontinuation of treatment.

Less frequently reported adverse reactions are vaginal bleeding, vaginal discharge, menstrual irregularities and skin rash. Usually these have not been of sufficient severity to require dosage reduction or discontinuation of treatment.

Increased bone and tumor pain and, also, local disease flare have occurred, which are sometimes associated with a good tumor response. Patients with increased bone pain may require additional analgesics. Patients with soft tissue disease may have sudden increases in the size of preexisting lesions, sometimes associated with marked erythema within and surrounding the lesions and/or the development of new lesions. When they occur, the bone pain or disease flare are seen shortly after starting NOLVADEX and generally subside rapidly.

Other adverse reactions which are seen infrequently are hypercalcemia, peripheral edema, distaste for food, pruritus vulvae, depression, dizziness, light-headedness and headache. There have been infrequent reports of thromboembolic events occurring during NOLVADEX therapy. Since for cancer patients in general an increased incidence of thromboembolic events is known to occur, a causal relationship to NOLVADEX remains conjectural. An increased incidence has been reported when cytotoxins are combined with NOLVADEX.

If adverse reactions are severe, it is sometimes possible to control them by a simple reduction of dosage without loss of control of the disease.

OVERDOSAGE: Acute overdosage in humans has not been reported. Signs observed at the highest doses following studies to determine LD$_{50}$ in animals were respiratory difficulties and convulsions. No specific treatment for overdosage is known; treatment must be symptomatic.

DOSAGE AND ADMINISTRATION: One or two 10 mg tablets twice a day (morning and evening). In the three single agent adjuvant NOLVADEX studies noted above (See Clinical Pharmacology), NOLVADEX was administered for two years. The optimal duration of adjuvant therapy is not known.

HOW SUPPLIED: Tablets containing tamoxifen as the citrate in an amount equivalent to 10 mg of tamoxifen (round, biconvex, uncoated, white tablet identified with NOLVADEX 600 debossed on one side and a cameo debossed on the other side) are supplied in bottles of 60 tablets and 250 tablets. Protect from heat and light.

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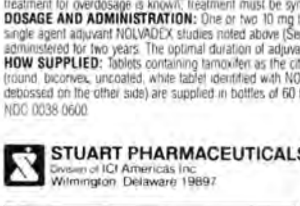

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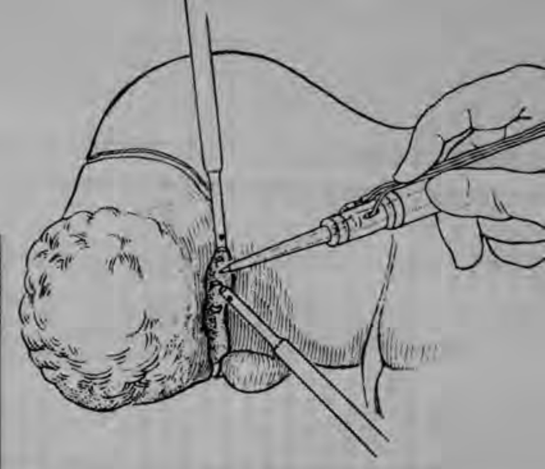
Now...the new book that shows you the role of surgical resection in the curative treatment of metastatic cancer



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Brief Summary of Prescribing Information

INDICATIONS For the relief of moderate to severe pain. NUBAIN can also be used for preoperative analgesia, as a supplement to surgical anesthesia, and for obstetrical analgesia during labor.

CONTRAINDICATIONS NUBAIN should not be administered to patients who are hypersensitive to it.

WARNINGS Drug Dependence NUBAIN has been shown to have a low abuse potential which is approximate to that of pentazocine. When compared with drugs which are not mixed agonist-antagonists, it has been reported that nalbuphine's potential for abuse would be less than that of codeine and propoxyphene. Psychological and physical dependence and tolerance may follow the abuse or misuse of nalbuphine. Therefore, caution should be observed in prescribing it for emotionally unstable patients, or for individuals with a history of narcotic abuse. Such patients should be closely supervised when long-term therapy is contemplated. Care should be taken to avoid increases in dosage or frequency of administration which in susceptible individuals might result in physical dependence. Abrupt discontinuation of NUBAIN following prolonged use has been followed by symptoms of narcotic withdrawal, i.e., abdominal cramps, nausea and vomiting, rhinorrhea, lacrimation, restlessness, anxiety, elevated temperature and piloerection. **Use in Ambulatory Patients** NUBAIN may impair the mental or physical abilities required for the performance of potentially dangerous tasks such as driving a car or operating machinery. Therefore, NUBAIN should be administered with caution to ambulatory patients who should be warned to avoid such hazards. **Use in Emergency Procedures** Maintain patient under observation until recovered from NUBAIN effects that would affect driving or other potentially dangerous tasks. **Use in Children** Clinical experience to support administration to patients under 18 years is not available at present. **Use in Pregnancy (other than labor)** Safe use of NUBAIN in pregnancy has not been established. Although animal reproductive studies have not revealed teratogenic or embryotoxic effects, nalbuphine should only be administered to pregnant women when, in the judgement of the physician, the potential benefits outweigh the possible hazards. **Use During Labor and Delivery** NUBAIN can produce respiratory depression in the neonate. It should be used with caution in women delivering premature infants. **Head Injury and Increased Intracranial Pressure** The possible respiratory depressant effects and the potential of potent analgesics to elevate cerebrospinal fluid pressure (resulting from vasodilation following CO_2 retention) may be markedly exaggerated in the presence of head injury, intracranial lesions or a pre-existing increase in intracranial pressure. Furthermore, potent analgesics can produce effects which may obscure the clinical course of patients with head injuries. Therefore, NUBAIN should be used in these circumstances only when essential, and then should be administered with extreme caution. **Interaction With Other Central Nervous System Depressants** Although NUBAIN possesses narcotic antagonist activity, there is evidence that in nondependent patients it will not antagonize a narcotic analgesic administered just before, concurrently, or just after an injection of NUBAIN. Therefore, patients receiving a narcotic analgesic, general anesthetics, phenothiazines, or other tranquilizers, sedatives, hypnotics, or other CNS depressants (including alcohol) concomitantly with NUBAIN may exhibit an additive effect. When such combined therapy is contemplated, the dose of one or both agents should be reduced. **Sulfites Sensitivity** NUBAIN contains sodium metabisulfite, a sulfite that may cause allergic-type reactions (e.g., hives, itching, wheezing, anaphylaxis) in certain susceptible persons. Although the overall prevalence of sulfite sensitivity in the general population is probably low, it is seen more frequently in asthmatics or in atopic nonasthmatic persons.

PRECAUTIONS Impaired Respiration At the usual adult dose of 10 mg/70 kg, NUBAIN causes some respiratory depression approximately equal to that produced by equal doses of morphine. However, in contrast to morphine, respiratory depression is not appreciably increased with higher doses of NUBAIN. Respiratory depression induced by NUBAIN can be reversed by NARCAN® (naloxone hydrochloride) when indicated. NUBAIN should be administered with caution at low doses to patients with impaired respiration (e.g., from other medication, uremia, bronchial asthma, severe infection, cyanosis or respiratory obstructions). **Impaired Renal or Hepatic Function** Because NUBAIN is metabolized in the liver and excreted by the kidneys, patients with renal or liver dysfunction may overreact to customary doses. Therefore, in these individuals, NUBAIN should be used with caution and administered in reduced amounts. **Myocardial Infarction** As with all potent analgesics, NUBAIN should be used with caution in patients with myocardial infarction who have nausea or vomiting. **Biliary Tract Surgery** As with all narcotic analgesics, NUBAIN should be used with caution in patients about to undergo surgery of the biliary tract since it may cause spasm of the sphincter of Oddi.

ADVERSE REACTIONS The most frequent adverse reaction in 1066 patients treated with NUBAIN is sedation 381 (36%). Less frequent reactions are sweaty/clammy 99 (9%); nausea/vomiting 68 (6%); dizziness/vertigo 58 (5%); dry mouth 44 (4%); and headache 27 (3%). Other adverse reactions which may occur (reported incidence of 1% or less) are: **CNS Effects** Nervousness, depression, restlessness, crying, euphoria, floating, hostility, unusual dreams, confusion, faintness, hallucinations, dysphoria, feeling of heaviness, numbness, tingling, unreality. The incidence of psychotomimetic effects, such as unreality, depersonalization, delusions, dysphoria and hallucinations has been shown to be less than that which occurs with pentazocine. **Cardiovascular** Hypertension, hypotension, bradycardia, tachycardia. **Gastrointestinal** Cramps, dyspepsia, bitter taste. **Respiration** Depression, dyspnea, asthma. **Dermatological** Itching, burning, urticaria. **Miscellaneous** Speech difficulty, urinary urgency, blurred vision, flushing and warmth. **Patients Dependent on Narcotics** Patients who have been taking narcotics chronically may experience withdrawal symptoms upon the administration of NUBAIN. If unduly troublesome, narcotic withdrawal symptoms can be controlled by the slow intravenous administration of small increments of morphine, until relief occurs. If the previous analgesic was morphine, meperidine, codeine, or other narcotic with similar duration of activity, one-fourth of the anticipated dose of NUBAIN can be administered initially and the patient observed for signs of withdrawal, i.e., abdominal cramps, nausea and vomiting, lacrimation, rhinorrhea, anxiety, restlessness, elevation of temperature or piloerection. If untoward symptoms do not occur, progressively larger doses may be tried at appropriate intervals until the desired level of analgesia is obtained with NUBAIN. **Management of Overdosage** The immediate intravenous administration of NARCAN® (naloxone hydrochloride) is a specific antidote. Oxygen, intravenous fluids, vasopressors and other supportive measures should be used as indicated. The administration of single doses of 72 mg of NUBAIN subcutaneously to eight normal subjects has been reported to have resulted primarily in symptoms of sleepiness and mild dysphoria.

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1. Schmidt WK, Tam SW, Shotzberger GS, et al: Nalbuphine. *Drug and Alcohol Dependence* 1985;14:339-362.
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Please see adjacent page for brief summary of prescribing information

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August 1987
Volume 206, Number 2

Annals of
Surgery

Malignant Carcinoid Tumors

An Analysis of 103 Patients with Regard to Tumor Localization, Hormone Production, and Survival

INGRID NORHEIM, M.D.,[*] KJELL ÖBERG, M.D.,[*] ELVAR THEODORSSON-NORHEIM, M.D.,[†]
PER GUNNAR LINDGREN, M.D.,[‡] GUDMAR LUNDQVIST, M.D.,[§] ANDERS MAGNUSSON, M.D.,[‡] LEIF WIDE, M.D.,[§]
and ERIK WILANDER, M.D.[||]

In a prospective study of 103 patients with carcinoid tumors consecutively referred for medical treatment, the most common sites of the primary tumors were the ileum (73%), bronchi (7%), and jejunum (4%). All patients had local metastases, and 96 (93%) also had liver metastases. The most common initial symptoms were diarrhea (32%), ileus (25%), and flush (23%). The overall frequency of diarrhea was 84% and of flush was 75%. Heart insufficiency caused by cardiac valve disease was seen in 33% of the patients. The carcinoid syndrome, including flush, diarrhea, and elevated urinary 5-hydroxyindole acetic acid (5-HIAA) concentrations, was manifested by 69 patients (67%), 64 of whom (93%) had carcinoid tumors of mid-gut origin. Elevated urinary 5-HIAA was found in 91 patients (88%), of which 89 displayed liver metastases. The plasma concentration of the tachykinin neuropeptide K (NPK) was elevated in 67 patients (66%), 63 of whom had tumors of the mid-gut region. Serum pancreatic polypeptide (PP) and human chorionic gonadotrophin α levels were elevated in 43% and 28% of the patients, respectively, and the highest levels were found in patients with metastatic bronchial carcinoid tumors. Thirty-nine of the 103 patients are now dead; 18 died of tumor progression, whereas 14 patients died of heart failure secondary to a carcinoid tricuspidal valve insufficiency. The estimated median survival from the time of histologic diagnosis was 14 years, and from the time of carcinoid syndrome was 8 years.

From the Department of Internal Medicine, University Hospital, Uppsala,[*] the Department of Clinical Chemistry, Karolinska Hospital, Stockholm,[†] the Department of Diagnostic Radiology,[‡] the Department of Clinical Chemistry,[§] and the Department of Pathology,[||] University Hospital, Uppsala, Sweden

THE CARCINOID TUMOR is a neuroendocrine neoplasm with malignant potential and the most frequent of all endocrine gut tumors. When liver metastases have appeared, the hormone secretion from the tumor cells may induce characteristic symptoms of flush, diarrhea, bronchial obstruction, and failure of the right side of the heart. The mechanisms behind the symptoms are not fully known, but serotonin might be a factor involved in diarrhea[1] and the flush might be induced by kallikrein-bradykinin,[2] or by ta-

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Supported by the Swedish Cancer Research Fund (1925-B84-10x and 1665-B84-03x), Pharmacia Research Fund, Swedish Medical Research Council (03x-07464), Nordisk Insulinfond, Swedish Society for Medical Sciences, Smith, Kline & French, Åke Wibergs Fund, Konung Gustav V:s Jubileumsfond (85:464), and funds of the University of Uppsala.

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Submitted for publication: October 13, 1986.

chykinin[3,4] secretion from the tumor cells. Secretion of prostaglandins[5] and histamine[6] also have been associated with carcinoid tumors. Acromegaly and Cushing's syndrome have been reported in patients with carcinoid tumors,[7–9] possibly caused by ectopic secretion of releasing factors from the tumor.[10]

The current study reports data from 103 patients with carcinoid tumors who were consecutively referred to our unit for evaluation. All patients were thus seen at one clinic, by the same physicians, and evaluated according to the same protocols. Special attention was paid to the localization of the primary tumor, metastases, and circulating tumor markers.

Patients

The study includes 103 patients (57 women and 46 men) with carcinoid tumors, seen at the Endocrine Unit of the Department of Internal Medicine, University Hospital, Uppsala, Sweden, during an 8-year period (January 1978–1986). The criterion for inclusion into the study was histologically and clinically verified metastatic carcinoid tumor. The Endocrine Unit serves as a referral unit for central Sweden, which has around 1 million inhabitants. Fifty-four of the patients (52%) in this series came from this region, and the annual incidence rate of individuals with metastatic carcinoid tumors was thus 0.7 patients/100,000 population. The incidence of the carcinoid syndrome was 0.5 patients/100,000 population/year. The remaining 49 patients were referred from other parts of Sweden, either because of an unusually complicated clinical picture or for evaluation for inclusion in clinical trials of specific medical treatments such as interferon.[11]

Altogether 69 patients had been subjected to operation before referral, and an exploratory laparatomy was done at our hospital in an additional 17 patients. These operations were performed to resect the primary tumor, which was possible in 54 patients with intraabdominal tumors and in five patients with pulmonary carcinoid tumors. If a recent tumor specimen from an operation was not available for histopathologic examination, a needle biopsy was executed from liver metastases. Thus, in all patients, the diagnosis of carcinoid tumor was based on a histopathologic examination. The diagnosis of a carcinoid tumor was established before operation in 40 of the 86 patients who had operation (47%), based on histopathology and/or elevated urinary 5-hydroxyindole acetic acid (5-HIAA) concentrations.

Methods

Routine investigations of blood and urine, including hemoglobin content, leucocyte and platelet counts, liver enzymes, serum creatinine, albumin, electrolytes, and fasting blood glucose were performed. The thyroid function was investigated by serum thyroid-stimulating hormone (TSH), thyroxine, and thyroid binding protein. An intravenous glucose tolerance test[12] was performed in 81 patients. Serum pancreatic polypeptide (PP) was determined in 96 patients, human chorionic gonadotrophin α and β subunits (HCG α and β) was determined in 102 patients.[13,14] Serum calcitonin concentrations were measured in 102 patients and gastrin levels were measured in 96 patients.[15,16] The plasma neuropeptide K (NPK) concentration was determined in 101 patients by a newly established radioimmunoassay.[17] Reference values are given in Table 7. The blood samples were drawn in the morning after an overnight fast, and the concentrations at the first visit to our clinic are reported. However, as the technique for NPK analysis is recent, it was impossible to determine its concentration in plasma from the first visit in 30 patients. In these cases the first evaluated plasma sample is used instead.

The urinary 5-HIAA excretion was determined[18] as an average of two 24-hour samples in all patients. Urinary cortisol was analyzed using a commercial radioimmunoassay (Farmos Group, Stockholm, Sweden) in a 24-hour sample of urine.

Computerized tomography (CT scan) and/or ultrasonography techniques were used in 101 patients for evaluation of metastatic disease to the liver. Two patients were not evaluated by these techniques; however, liver metastases were seen at operation in both patients. Ultrasonically guided needle (diameter 2.1 mm) biopsy from the liver metastases was obtained in 90 patients using a previously described technique.[19] In 42 patients with unknown primary tumor location, an angiography of the celiac and mesenteric arteries was performed. All patients were evaluated by roentgenography of the lungs. When the patients had local symptoms from the skeleton, scintigraphy and roentgenography were carried out. Bone marrow aspiration for evaluation of metastases was performed in only a small number of patients. Echocardiography of the heart to detect valvular involvement was performed in 70 patients.

Tumor tissue specimens (N = 103) were stained with hematoxylin and eosin, and investigated morphologically for homogeneous cell structures and characteristic growth patterns of endocrine tumors. For further identification of the tumor as a neuroendocrine neoplasm, the Grimelius (N = 101),[20] Masson (N = 96),[21] and Sevier–Munger (N = 42)[22] silver staining techniques were used. In addition, a technique with monoclonal antibodies for serotonin was used in specimens from 47 patients.[23]

Statistical Analysis

Nonparametric statistical methods as described by Conover[24] were used throughout the study. The median and interquartile ranges were used as indicators of central tendency and variation, respectively. The Mann-Whitney test was used to test for differences between two independent groups. The estimated median survival was calculated as described by Colton.[25]

TABLE 1. *The Median Age at the Time of Diagnosis and the Sex of 103 Patients with Metastatic Carcinoid Tumors Related to the Localization of the Primary Tumor*

Location	Median Age (range)* (years)	Males/ Females
Mid-gut (-appendix)	61.0 (52–68)	40/48
Appendix	38.0 (26–50)	0/2
Thoracal	52.5 (29–60)	5/3
Unknown	60.0 (53–61)	1/2
Duodenum	57.0	0/1
Rectum	51.0	0/1
Total	59.0 (51–66)	46/57

* Variation given as the interquartile range.

Results

The Primary Tumor and Metastases

The median age at diagnosis for all patients was 59 years (interquartile range: 51–66 years). The patients with appendical and bronchial carcinoid tumors (Table 1) were younger at the time of diagnosis than the remainder (median age: 38 and 52 years, respectively). A slight predominance of women was seen in the total group (females/males: 57/46).

In 75 patients (73%) the primary tumor was localized to the ileum (Table 2), whereas four patients had jejunal carcinoid tumors, three had cecal tumors, and two had appendical carcinoid tumors. In nine patients the location of the primary tumor was unknown, but six of them probably had tumors of mid-gut origin because of typical histopathologic examination and a positive silver staining with the Masson technique. Thus, 90 of 103 patients (87%) presumably had a mid-gut carcinoid tumor. Intrathoracal carcinoid tumors were found in eight patients; seven had bronchial tumors and one had a mediastinal (thymic?) tumor. The surgeons believed the excision to be radical in only six of the 86 patients who had operation. Five of these patients had a primary tumor of less than 2 cm in diameter. However, liver metastases developed later in all these patients who were considered surgically cured. In 16 patients (17%) multiple primary tumors in the small intestines were found. Local metastases were verified in all patients, and 96 (93%) also had metastases to the liver (Table 3).

Peripheral metastases to sites other than the liver were seen in 31 patients (30%). Of the eight patients with intrathoracal tumors and liver metastases, five revealed metastases to the skeleton and one had metastases to the pituitary gland.

Symptoms and Delay in Diagnosis

Diarrhea was most frequently the first symptom, prompting 33 patients (32%) to consult a physician (Table 4). The second most common initial symptoms were ileus/subileus (25%) and flush (23%). The median duration of any symptoms before diagnosis was 1 year (interquartile range: 0.5–3 years). The patients with subileus/ileus as the first symptom had the shortest delay before diagnosis, *i.e.*, median 0.6 years (interquartile range: 0–3 years). The median time from the onset of diarrhea until diagnosis was 1.5 years (interquartile range: 1–4 years). The patients with flush had a median delay of 2 years (interquartile range: 1–4 years).

Table 5 illustrates the total number of patients with symptoms of diarrhea, flush, intestinal obstruction, tricuspidal heart failure, and asthma. Altogether 69 patients (67%) had a complete carcinoid syndrome with flush, diarrhea, and elevated urinary 5-HIAA concen-

TABLE 2. *Location of the Primary Tumor Related to Symptoms of Flush and Diarrhea, and Elevated Levels of Urinary 5-HIAA and Plasma NPK.*

Origin	Total (%)	Flush	Diarrhea	5-HIAA	NPK	Carcinoid Syndrome (%)*
Ileum	75 (73.0)	61	68	67	51	54 (72)
Jejunum	4 (3.9)	2	2	4	2	2 (50)
Cecum	3 (2.9)	3	3	3	3	3 (100)
Appendix	2 (1.9)	1	1	2	1	1 (50)
Bronchial	7 (6.8)	3	4	5	2	3 (43)
Mediastinum	1 (0.9)	0	0	1	0	0
Duodenum	1 (0.9)	1	1	1	0	1 (100)
Rectum	1 (0.9)	0	0	0	0	0
Unknown peripheral	3 (2.9)	1	2	2	2	1 (33)
Unlocalized mid-gut	6 (5.9)	5	5	6	6	4 (66)
Mid-gut tumor	90 (87.4)	72	79	82	63	64 (71)
Total	103 (100.0)	77	86	91	67	69 (67)

* Number and percentage of patients with complete carcinoid syndrome.

TABLE 3. *The Localization of Metastases in 103 Patients with Carcinoid Tumors*

Metastases	No. of Patients	%
Local	103	100.0
Liver	96	93.0
Skeleton	14	13.6
Peripheral lymph gland	7	6.7
Ovarian	4	3.6
Lung	2	1.9
Skin	1	0.9
Pancreas	1	0.9
Pleural	1	0.9
Pituitary gland	1	0.9

trations (Table 2 and Table 5). In the patients with mid-gut carcinoid tumors, the syndrome was seen in 64 patients (62%). A total of 70 patients (68%) had symptoms of both flush and diarrhea, and 12 of them also had asthmatic attacks. One of these patients with flush and diarrhea had no liver metastases and normal urinary 5-HIAA excretion. The remainder had both liver metastases and elevated urinary 5-HIAA excretion. Four patients (4%) had only flushing and 14 (14%) had only diarrhea. Asthma, which occurred in 15 patients (15%), was not seen as a sole symptom in any patient. Four patients (4%) with intrathoracic tumors had symptoms of invasive growing neoplasm, but no carcinoid symptoms such as flush or diarrhea, and they also had normal urinary 5-HIAA levels. Four patients (4%) with mid-gut tumors did not have any apparent symptoms, and in these patients the primary tumor was detected during operation for ileus.

Thirty-four patients (33%) with cardiac insufficiency had systolic murmur and signs of abnormal tricuspidal valve function at echocardiography. All these patients, except one patient with unknown tumor localization, had carcinoid tumors of mid-gut origin. Only one patient had valve replacement. Thirty patients had a complete carcinoid syndrome and four had diarrhea but no flush. The median age of these patients at the time of diagnosis was 60 years and the median duration of flush and/or diarrhea was 2 years.

TABLE 4. *Initial Symptoms in 103 Patients with Carcinoid Tumors*

			Delay of Diagnosis (Years)	
First symptom	No. of Patients	%	Median	Interquartile Range
Diarrhea	33	32	1.5	(1–4)
Ileus/subileus	26	25	0.6	(0–3)
Flush	23	23	2.0	(1–4)
Pain	10	10		
Cough	2	2		
Asthma	2	2		
Loss of weight	2	2		
Melena	1	1		
No symptoms	3	3		
Unknown	1	1		
Total	103		1	(0.5–3)

TABLE 5. *Clinical Symptoms at Referral in 103 Patients with Carcinoid Tumors*

Symptoms	No. of Patients	%
Diarrhea	86	84
Flush	77	75
Ileus/subileus	45	44
Cardiac insufficiency	34	33
Asthma	15	15
Carcinoid syndrome*	69	67

* Includes flush, diarrhea, and elevated levels of urinary 5-HIAA.

CT Scan and Ultrasound Investigations

Abdominal CT scans were performed in 96 patients (93%) and the ultrasound technique was used in 96 patients (93%). One or both techniques were used in evaluating 101 patients, and metastases to the liver were found in 93 patients (92%). At operation, an additional three patients had small miliary metastases in the liver. Multiple liver metastases were found in 73 patients. The size of the liver metastases varied from miliary lesions undetectable by CT scan to large metastases, with a diameter of 10–12 cm, often with central necrosis. On CT scan the metastases had a low attenuation, whereas by ultrasound the echodensity varied considerably.

Histopathology

All tumors had the characteristic growth patterns of endocrine tumors at histopathologic examination. The mid-gut tumors, except one appendical carcinoid tumor, contained homogeneous cells with insular-like growth patterns. A positive staining using the Grimelius silver staining technique was noted in 101 evaluated specimens (Table 6). A positive reaction was found in 83 (88%) of the 96 tumor specimens evaluated with the Masson staining technique. Six of nine tumors of unknown origin had the characteristic growth pattern of mid-gut carcinoid tumors and positive staining using the Grimelius and the Masson techniques. These tumors were therefore presumably of mid-gut type. Negative staining with the Masson technique was found in all bronchial tumors, the mediastinal, the rectal, and three tumors of unknown localization outside the mid-gut. One appendical carcinoid tumor with uncharacteristic growth pattern stained neither with the Masson silver staining technique nor with the specific monoclonal antibodies against serotonin. The rest of the tested mid-gut

TABLE 6. *Histopathologic Investigations of Tumor Specimens Using Different Silver Staining Techniques and Serotonin Immunohistochemical Staining, Related to the Localization of the Primary Tumor*

Primary Tumor Localization	Total No.	Grimelius +	Masson +	Masson −	Sevier-M +	Sevier-M −	Serotonin +	Serotonin −
Mid-gut	88	88	82	1	30	0	42	1
Bronchial	7	7	0	7	4	2	(1)	2
Mediastinal	1	1		1		1		
Unknown	3	3	0	3	3	0		1
Rectum	1	1		1		1		
Duodenum	1	1	1		1			
Total	101	101	83	13	38	4	43	4

tumors had a positive staining with both these techniques.

Tumor Markers

Elevated levels of urinary 5-HIAA were present in 91 patients (88%) (Tables 2 and 7). The median 5-HIAA level was 360 μmol/24 hours (range: 30–3370). Patients with carcinoid tumors located in the mid-gut had a median value similar to that of the whole group, and individuals with bronchial tumors generally had a higher value (median: 480 μmol/24 hours [range: 29–1436]) (Fig. 1). Plasma NPK was elevated in 67 patients (66%) with a median plasma level of 25 pmol/L (range: 7.8–2023). Sixty-three of them (94%) had tumors of the mid-gut type, whereas patients with carcinoid tumors of thoracal origin or of other unusual localizations (Table 2) had plasma NPK median levels close to the normal range (Fig. 2).

The serum PP level was elevated in 43% of the patients, median 0.4 ng/mL (range: 0.03–155). HCG α was above the reference range in 28%; median for men and premenopausal women was 1.5 μg/L (range: 0.34–390), and median for postmenopausal women was 6.15 μg/L (range: 0.41–1500). The highest levels of PP and HCG α were found in patients with bronchial carcinoid tumors (Figs. 3 and 4). A slightly elevated serum gastrin level was observed in 14 patients (15%), and HCG β and calcitonin levels were elevated in 12 and four patients, respectively (Table 7).

TABLE 7. *Tumor Secretory Products ("Markers") in Patients with Carcinoid Tumors*

"Tumor marker"	N	%	Median Value (mean)	Normal Range
5-HIAA	91/103	88	360 (560)	<80 μmol/24 h
NPK	67/101	66	25 (99)	<12 pmol/L
PP	41/95	43	0.4 (2.4)	<0.4 ng/mL
HCG α	29/102	28	6.2* (33.7)	<8.5 μg/L
			1.5‡ (14.9)	<3.0 μg/L
Gastrin	14/96	15	25 (51.6)	<55 pmol/L
HCG β	12/102	12	1.0 (1.43)	<2.5 μg/L
Calcitonin	4/82	4		<290 pmol/L

* Postmenopausal women.

† Mean and premenopausal women.

In eight patients (8%) elevated levels of all four principal markers, 5-HIAA, NPK, PP, and HCG α were

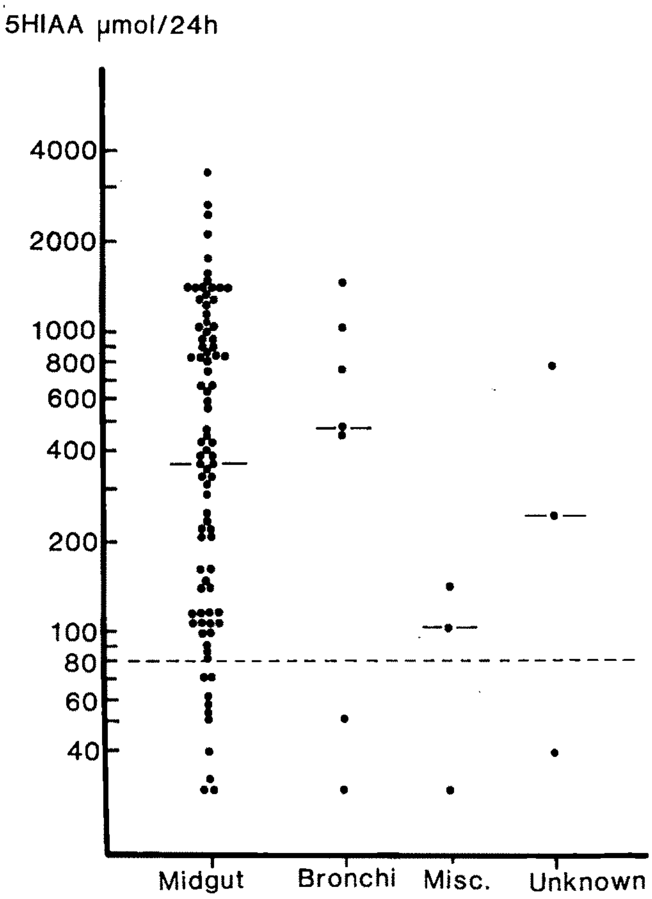

FIG. 1. The urinary 5-HIAA excretion in patients with carcinoid tumors originating in the mid-gut (N = 90), bronchi (N = 7), unknown site outside mid-gut (N = 3) and miscellaneous: mediastinum (N = 1), rectum (N = 1), and duodenum (N = 1). Reference value for 5-HIAA < 80 μmol/24 h.

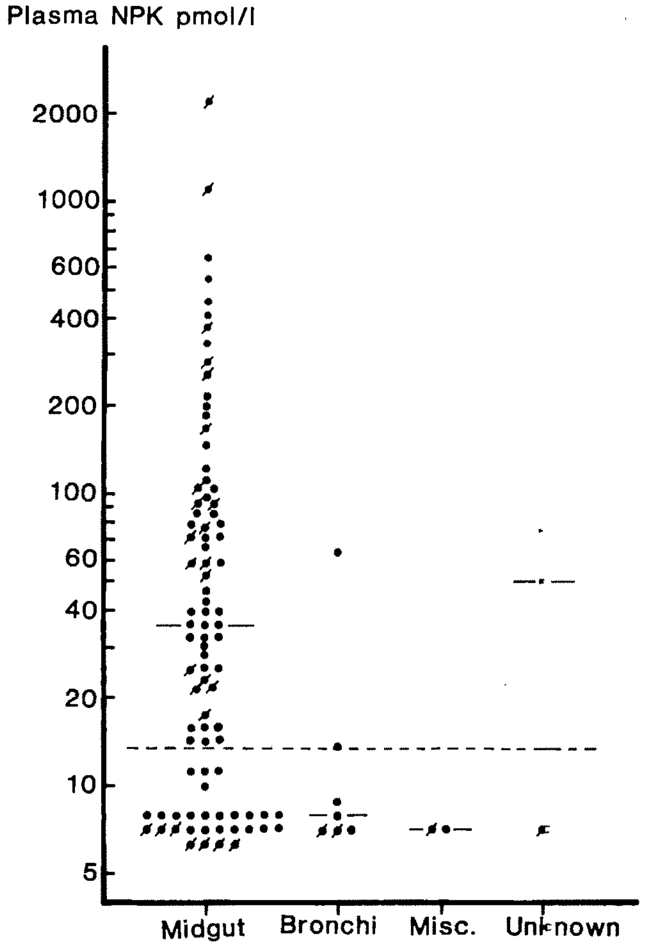

FIG. 2. The concentrations of NPK in plasma from carcinoid patients related to the localization of the primary tumor. Reference level for NPK < 12 pmol/L. NPK concentrations not taken at first visit are marked.

found (Table 8). Only three of 103 patients (3% had no measurable tumor marker in blood or urine, and no patients had metastases to the liver.

The patients with diarrhea had somewhat higher median values for 5-HIAA and NPK than the whole group of carcinoid patients (Table 8, Figs. 5 and 6). The patients with flush had significantly ($p < 0.05$) higher levels of 5-HIAA excretion and plasma concentration of NPK than the whole group. The highest levels of 5-HIAA and NPK were seen in the group of patients who had failure of the right side of the heart and tricuspidal valve insufficiency. The median value for 5-HIAA was 885 μmol/24 hours and for NPK was 75 pmol/L. These levels were significantly higher ($p < 0.01$) than in the whole group of patients.

Clinical and Laboratory Screening

At the first referral to the hospital, 28 patients (27%) had advanced disease with a median weight loss of 10 kg (interquartile range: 7–17 kg) together with a palpable liver-edge more than 5 cm below the right costal margin. Of these patients, 17 are now dead. Nineteen patients (18%) had anemia (B-hemoglobin < 110 g/L). Thirty-six patients (35%) had a sedimentation rate above 20 mm/h, and 15 (14.5%) had leukopenia ($<4.0 \times 10^9$/L). Platelet counts of less than 150×10^9/L were found in 10 patients (9%) (Table 9). Elevated serum levels of the enzymes, ASAT, ALAT, lactate dehydrogenase, as well as serum alkaline phosphates and bilirubin were present in 22 patients. Thirteen patients (12%) showed abnormality in three of the four liver function tests, and all these patients had a liver enlarged by more than 5 cm below the right costal margin. Eleven of these patients are now dead. Twenty-seven of 45 patients with palpable liver had one or more abnormal liver function tests. Serum albumin level below 34 g/L was found in 38 patients (37%). All patients had normal serum levels of sodium, potassium, and chloride.

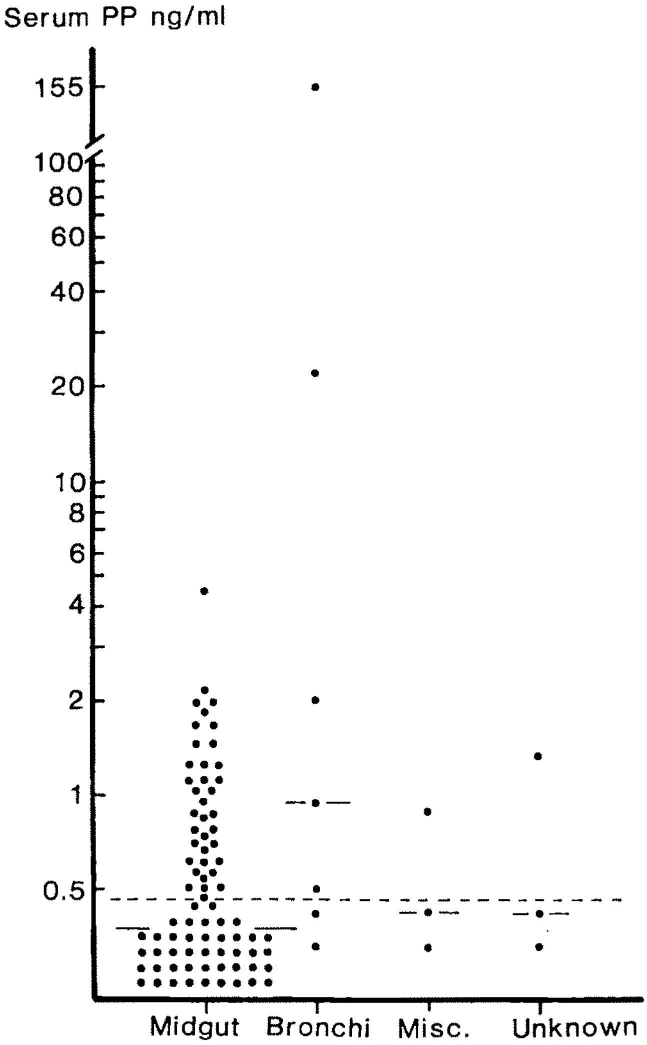

FIG. 3. The concentrations of pancreatic polypeptide (PP) in serum from patients with carcinoid tumors, related to the localization of the primary tumor. Reference level for PP < 0.4 ng/mL.

Additional Endocrine Diseases

Five patients had been treated earlier for hyperthyroidism, and a nodular goiter was found in four patients. Four patients had insulin-dependent diabetes mellitus. Endocrine screening revealed three patients with hypothyroidism and one with a primary hyperparathyroidism, verified by surgery. One patient with a bronchial carcinoid tumor had Cushing's syndrome developed probably as a result of ectopic corticotropin releasing factor (CRF) production in the tumor.

Accessory Tumor Diseases

An accessory malignant tumor was seen in five patients (5%). Two patients had mammary carcinoma. Chronic myelogenic leukemia, rectal, and prostatic carcinoma were seen in three patients. The accessory tumor disease was diagnosed after the carcinoid tumor in three of the patients.

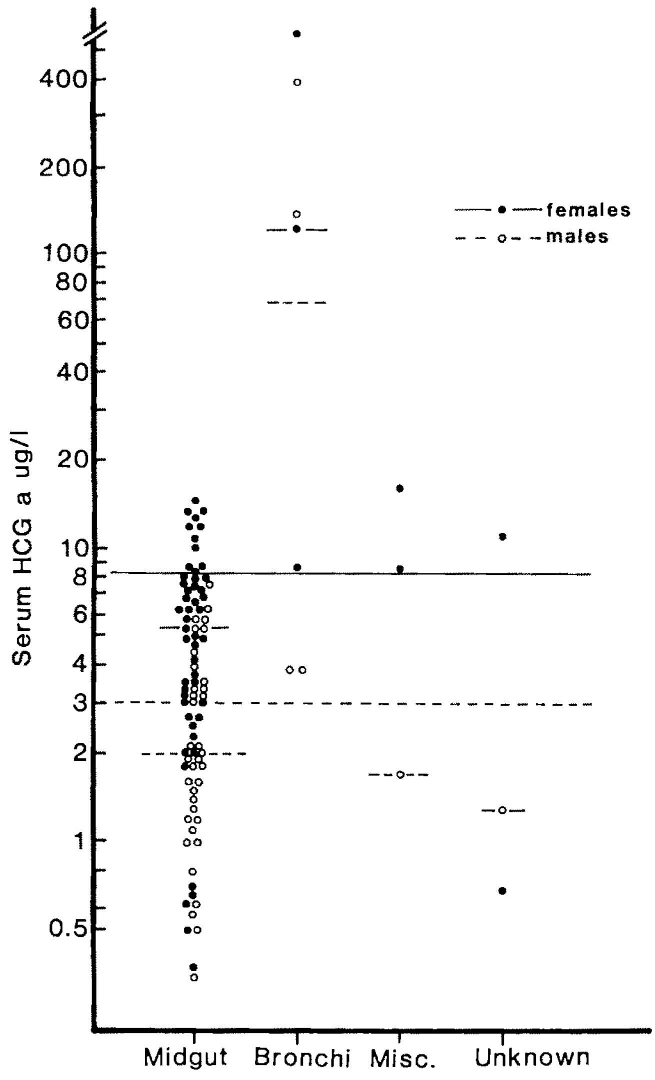

FIG. 4. The concentrations of HCG α in serum from patients with carcinoid tumors, related to localization of the primary tumor localization. Reference level for HCG α men and premenopausal women < 3.0 μg/L; postmenopausal women < 8.5 μg/l.

TABLE 8. *The Median Concentrations of 5-HIAA and NPK in Relation to the Clinical Symptoms in the Patients*

Signs	N	5-HIAA (μmol/24 hours)*	NPK (pmol/L)*
Diarrhea	86	425 (178–1038)	35 (11–91)
Flush	77	539 (210–1050)	41 (17–101)
Cardiac	34	885 (683–1395)	76 (25–219)

* Numbers in parentheses are variations given as interquartile ranges.

Survival

The median time from histologically diagnosed carcinoid tumor until referral to our unit for evaluation, the doctor's delay, was 0.5 years (interquartile range: 0.2–3.2 years).

Altogether 39 of 103 patients (38%) died during the observation period. Tumor progression was the cause of death in 18 patients (46%), whereas in 14 patients (36%) cardiac insufficiency was the main reason (Table 10). All

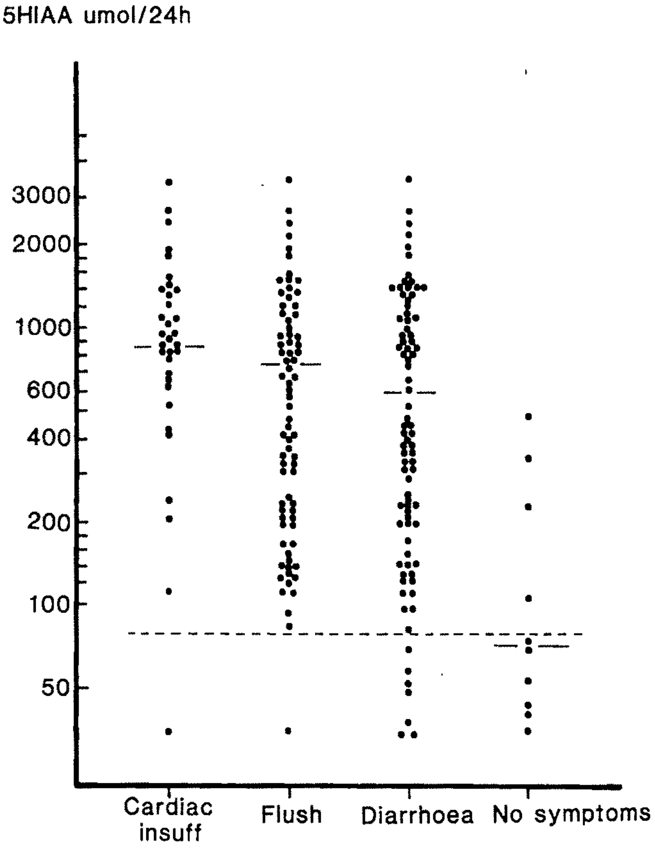

FIG. 5. The concentrations of urinary 5-HIAA excretion related to the symptoms in patients with carcinoid tumors.

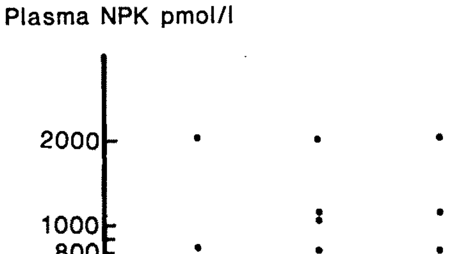

FIG. 6. The concentrations of NPK related to the patient's symptoms.

these patients also had an advanced tumor disease. The median time from carcinoid symptoms until death in these 39 deceased patients was 3.5 years, and the median time from histologic diagnosis was 2 years For the whole patient group, the estimated 5-year survival rate from the time of histologic diagnosis was 65% and from the time of definitive symptoms of a carcinoid syndrome, flush, or diarrhea was 67% (Figs. 7 and 8). Estimated median survival from the time of histologic diagnosis was 14 years, and from the time of carcinoid syndrome was 8 years. The survival curves are not adjusted for the age of the patients.

TABLE 9. *The Number of Patients with Abnormal Routine Laboratory Parameters*

Test	Reference Level	No. of Patients	%
Hemoglobin	<110 g/L	19	18
Sedimentation rate	>20 mm	36	35
ASAT	>0.6 μkat/L	15	14
ALAT	>0.6 μkat/L	18	17
Alkaline phosphatase	>4.8 μkat/L	22	21
Lactat dehydrogenase	>6.7 μkat/L	16	15
Bilirubin	>20 μmol/L	6	6
Leukocyte particle concentration	<4 × 10^9/L	15	14
Leukocyte particle concentration	>9 × 10^9/L	6	6
Thrombocyte particle concentration	<150 × 10^9/L	10	9
Thrombocyte particle concentration	>400 × 10^9/L	8	7
Creatinine	>106 μmol/L	5	4
S-albumin	<34 g/L	38	37
S-calcium	>2.6 mmol/L	5	4

TABLE 10. *Causes of Deaths in 39 Deceased Patients (Of 103 Patients) with Carcinoid Tumors*

Causes of Death	N	%
Tumor progression	18	45.2
Cardiac insufficiency	14	36.0
Myocardial infarction	1	2.5
Intestinal necrosis	1	2.5
Cushing's syndrome	1	2.5
Pulmonary emboli	1	2.5
Sepsis	1	2.5
Unknown	2	5.3
Total	39	

Discussion

Carcinoid tumors, originally described by Oberndorfer[26] in 1907, have proved to be a heterogeneous group of tumors. However, Williams and Sandler,[27] in 1963, proposed that carcinoids arising in three areas: the fore-gut (bronchi, stomach, duodenum), mid-gut (jejunum, ileum, appendix, and proximal colon) and hind-gut (distal colon and rectum), form three distinct groups based on histologic, biochemical, and clinical evidence. The relevance of this subdivision in the clinical situation, however, has to be further evaluated. The expression of clinical symptoms as well as the hormone production may vary among patients with different categories of carcinoid tumors. Furthermore, there are considerable differences in clinical symptoms, hormone production, and tendency to become malignant even in tumors within the same group, *e.g.*, the appendical carcinoid tumor, which is the most frequent carcinoid tumor, rarely becomes malignant or induces clinical symptoms caused by hormone production, whereas ileal carcinoid tumors often give rise to metastases and the carcinoid syndrome.[28] Thus, carcinoid tumors, which are the most frequent neuroendocrine tumors, deserve careful assessment and discerning management.

In the current prospective study of a large number of patients with carcinoid tumors, we have concentrated on hormone production related to localization of the carcinoid tumors and metastases. All patients, who were consecutively referred to our unit during an 8-year period, were investigated according to the same procedure.

In agreement with other studies that were done retrospectively, the majority of our patients with metastatic carcinoid tumors had mid-gut tumors.[28,29] As the patients were referred for treatment of clinical symptoms, *e.g.*, carcinoid syndrome, it is not surprising that most of the tumors were of mid-gut origin, since mid-gut carcinoid tumors most often display hormone-related clinical symptoms.

The annual incidence rate of metastatic carcinoid tumors in our study was 0.7 patients/100,000 population, and the annual incidence of the carcinoid syndrome was 0.5/100,000. This is less than found in the necropsy study by Berge and Linell[30] who demonstrated an annual incidence of malignant carcinoid tumors of 2.1 patients/100,000 population. The true annual incidence of clinically significant tumors is likely to be somewhere between the results of these two studies. Our clinical study may underestimate the true frequency because patients with only local metastases are treated surgically and thus not referred and very old individuals with metastatic tumors are rarely referred to our clinic. The average age of 59 years at the time of diagnosis is in agreement with other studies.[28,31] The lower onset ages of appendical and pulmonary carcinoid tumors is also in accordance with earlier studies.[31]

Our data emphasize the difficulty in determining the surgical curability at the time of the primary operation. Even in patients with small primary tumors (diameter < 2 cm) that are considered to be radically removed, metastatic carcinoid disease may later develop. However, appendical carcinoid tumors, which are often small (less than 2 cm) and frequently incidentally found at operation for appendicitis, seldom develop metastases. Only two of our patients with metastatic carcinoid disease had the primary tumor located to the appendix. This may support the suggestion that appendical carcinoid tumors originate from neuronal cells instead of the enterochromaffin cells,[32,33] which are the source of other mid-gut carcinoid tumors. The majority (93%) of our patients had liver metastases, but unusual localizations of metastases, such as the skeleton, the ovary, and the pituitary, were also found. These unusual localizations frequently occurred in patients with tumors of fore-gut origin.

The most frequent initial symptom was diarrhea (32%), followed by symptoms of intestinal obstruction (25%) and flushing (23%). The relative predominance of diarrhea and flushing in our material may be due to the high frequency of patients with the carcinoid syndrome (67%). The delay between initial symptom and diagnosis was shortest in patients with symptoms of intestinal obstruction (0.6 years), but considerably prolonged when the disease presented with flush and/or diarrhea (1.5–2 years).

The frequency of cardiac involvement was in the same range as found by Graham-Smith, who found cardiac involvement in 41% of patients with carcinoid syndrome.[34] All but one of our patients with tricuspidal valve disease had a primary tumor of mid-gut origin.

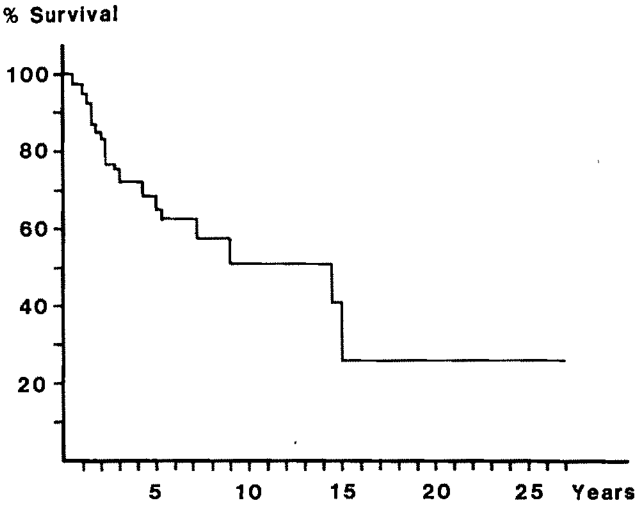

FIG. 7. Survival from the time of histologic diagnosis in patients with carcinoid tumors. The estimated 5-year survival rate was 65%.

The mean age at diagnosis of a carcinoid tumor and cardiac failure did not diverge from that of the rest of the patients, but the median duration of symptoms before referral and start of treatment was 2 years, which is somewhat longer than for other patients. The patients in whom carcinoid cardiac involvement developed presumably have hormonally active tumors, secreting a spectrum of biologically active substances, and the levels of urinary 5-HIAA and plasma NPK were significantly higher in this group than in all patients (Figs. 5 and 6). None of our patients with bronchial carcinoid tumors displayed cardiac valve disease, although these patients had high excretion of 5-HIAA in the urine. However, plasma NPK was not significantly increased in patients with bronchial carcinoid tumors and liver metastases (Fig. 2). Serotonin has been proposed earlier to be an etiologic factor for the development of carcinoid heart disease, including fibrosis of the cardiac valves. How-

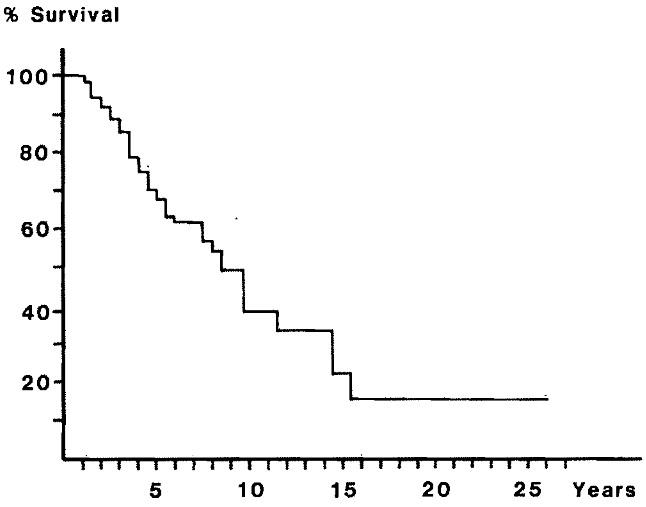

FIG. 8. Survival from the time of definite symptoms in patients with carcinoid syndrome. The estimated 5-year survival rate was 67%.

ever, tachykinins, such as neurokinin A and substance P, have recently been demonstrated to stimulate fibroblast growth,[35] and the same tachykinins are known to be secreted in a majority of our patients with mid-gut tumors. Thus, tachykinin-like substances might be etiologic agents for the fibrosis seen in the carcinoid heart disease.

There was a difference in tumor-secreted products between patients with mid-gut and fore-gut carcinoid tumors as stated previously. High levels of urinary 5-HIAA were seen in both groups, but NPK was predominantly recorded in patients with mid-gut tumors. HCG α and PP were found in high levels in patients with bronchial carcinoid tumors, whereas these peptides were only slightly elevated in the mid-gut group. This is in accordance with the theory of Williams and Sandler,[27] which proposed different origin and biochemistry of bronchial and ileal carcinoid tumors.

Flushing was seen in 77 patients; all but one patient had elevated urinary 5-HIAA, whereas 60 patients had elevated plasma NPK. Both serotonin and tachykinins are vasoactive substances that may be responsible for the carcinoid flush. However, the serotonin receptor antagonist (Ketanserin®) can eradicate the diarrhea but not the flush,[36] which indicates that serotonin cannot be the only mediator of flush. Furthermore, the somatostatin analogue SMS 201-995 (Sandoz Pharmaceuticals Corporation, Stockholm, Sweden) can block the carcinoid flush, and in parallel, reduce the plasma NPK levels, indicating a role of tachykinins in the etiology of flush (unpublished data). Similarly, plasma NPK is known to increase during spontaneous and pentagastrin stimulated flush.[4] In patients with malignant carcinoid tumor, urinary 5-HIAA and plasma NPK were the best "markers," especially in tumors of mid-gut origin.

Plasma concentrations of PP and HCG α have been reported earlier to be frequently elevated in patients with malignant carcinoid tumors.[37,38] However, in this more extended study, the frequency is somewhat lower, which might be explained by the fact that in the current study we have only reported the concentrations at the time of referral to the unit. However, the concentrations frequently increased with time. Another explanation might be that initially only advanced cases were referred, whereas more recently, many patients with less advanced disease have been sent to us.

Eighty-six patients had diarrhea, and of these patients, 79 had elevated urinary 5-HIAA and 61 had elevated plasma NPK. The diarrhea may possibly depend on the intestinal effects of serotonin secreted from the tumor,[36] but some patients may also display short-bowel syndrome after resection of intestinal carcinoid tumors. Local mechanical effects on the gut by the tumor itself cannot be ruled out as some patients had normal circulating serotonin levels and normal urinary 5-HIAA excretion.

Seven patients had no detectable metastases in the liver. However, two patients had elevated 5-HIAA excretion in the urine and symptoms of both flush and diarrhea, and one patient had elevated 5-HIAA excretion and no symptoms. In addition, one patient had elevated serum HCG α and diarrhea. Only three patients revealed no tumor markers to be followed and none of them had liver metastases. The lack of relation between symptoms, urinary 5-HIAA excretion, and liver metastases might depend on the detection limits of the CT scan and ultrasound techniques, which are unable to perceive lesions less than 0.5 cm in diameter. However, occasionally patients with carcinoid tumors of mid-gut origin may have the carcinoid syndrome in the absence of hepatic metastases.[39]

Most patients had normal results of routine laboratory tests. Elevated levels of liver enzymes, particularly alkaline phosphatases, occurred, especially in patients with large metastases in the liver, and among our patients, 11 of 13 with elevated levels of liver enzymes and enlarged liver are now dead. Thus, these findings together with loss of weight seem to be a poor prognostic factor.

An accessory malignant neoplasm was found in only five patients, which is a lower frequency than published in other reports: Barclay and Shapira reported a frequency of 17%[40] and Dawes et al. reported a frequency of 15%.[41] The Mayo Clinic study[28] had a second malignancy in 5% of patients, which is comparable with our findings. The differential diagnosis between carcinoid tumor, mammary cancer, and small cell lung cancer may be difficult in some instances, and the exact diagnosis frequently depends on the experience of the pathologist.

The prognosis of the patients with carcinoid tumors varies depending on the localization of the primary tumor and the stage of disease. In patients with only local metastases, Dawes et al.[41] found that 80% of the patients lived for 5 years. When liver metastases were present, the 5-year survival rate was 19–38%.[28,42,43] Our findings of an estimated 5-year survival rate of 65% in our patients with malignant carcinoid tumors seems interesting. Although different patient materials might not be compared, our data might indicate that new therapeutic alternatives such as interferon, which was used in 92 of the patients,[11] and new somatostatin analogues (SMS 201-995), which were used in about 15 patients, might add years to life and not only improve the quality of life. Besides earlier awareness and diagnosis of the disease, this might contribute to the better survival data.

In conclusion, the current prospective study of malignant carcinoid tumors demonstrates that mid-gut tumors, except appendical tumors, often become malignant, and that diarrhea and flushing are the most frequent clinical symptoms when liver metastases have appeared. Furthermore, cardiac insufficiency is often seen, especially in patients with mid-gut carcinoid tumors and carcinoid syndrome. Nearly all patients have one or more tumor-secreted products, which can be used as markers for both diagnosis and follow-up. Urinary 5-HIAA excretion is elevated in carcinoid tumors irrespective of the origin of the primary tumor, whereas levels of NPK is elevated mainly in patients with mid-gut carcinoid tumors. Fore-gut tumors, on the other hand, more often present high levels of HCG α and PP. The most frequent causes of death were tumor progression followed by carcinoid heart failure. Our survival data are somewhat more favorable than those earlier reported, which may indicate development of more effective therapeutic alternatives such as interferon and somatostatin analogues.

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Use of Tubes and Radiographs in the Management of Small Bowel Obstruction

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During the past 10 years 311 consecutive patients were admitted with 342 episodes of small bowel obstruction (SBO). There were 193 cases of partial small bowel obstruction (PSBO) and 149 cases of complete small bowel obstruction (CSBO) as determined by interpretation of the abdominal radiographs done on admission. The purpose of this review was to determine the reliability of the admission plain abdominal radiographs and subsequent upper gastrointestinal (UGI) contrast studies in predicting the need for operative intervention. The use of nasogastric tubes (NGT) *versus* nasointestinal (long) tubes (NIT) was correlated with the following outcome variables; length of hospital stay (LOS), timing of operative intervention, incidence of postoperative complications, and duration of postoperative ileus. Long tubes (NIT) were used in 64 episodes of PSBO and 81 episodes of CSBO, whereas nasogastric tubes (NGT) were used in 116 cases of PSBO and 68 cases of CSBO. Thirty-eight of 193 (19%) patients with PSBO required operation (20 of 116 with NGT and 18 of 64 with NIT), whereas 125 of 149 (84%) patients with CSBO required operation (60 of 68 with NGT and 65 of 81 with NIT). Need for operation was not correlated with whether or not long tubes passed beyond the pylorus; 50 passed *versus* 33 not passed in operative groups ($p = 0.15$). Twelve of 83 patients with NIT had operation within 24 hours *versus* 52 of 80 patients with NGT ($p < 0.001$). In six of 64 patients who had surgery within 24 hours, complications developed *versus* in 39 of 99 patients operated on more than 24 hours after admission ($p \leq 0.001$). In 29 of 83 patients treated with NIT, postoperative complications developed *versus* in 16 of 80 patients with NGT ($p \leq 0.04$). The mean duration of postoperative ileus in patients with NIT was 7 days *versus* 4.1 days for NGT patients ($p < 0.001$). The mean LOS was 12.2 days for NGT patients *versus* 21 days for patients with NIT ($p < 0.001$). Barium UGI contrast studies were performed in 57 patients to establish the presence of obstruction. In 34 of 57 patients the UGI disclosed mechanical obstruction that required operative intervention. In the remaining 23 patients no obstruction was demonstrated, and all 23 patients recovered without operation. In conclusion, there is no inherent superiority of NIT *versus* NGT in the treatment of SBO. Long tubes (NIT) were associated with a significantly greater LOS, duration of postoperative ileus, and incidence of postoperative complications, probably because of the significantly greater delay in operation in patients treated with NIT *versus* NGT. The radiographic distinction between PSBO and CSBO is clinically important in that 84% of patients with features of CSBO required operation *versus* only 19% of patients with PSBO.

THERE IS CONSIDERABLE controversy regarding both the effectiveness of tube decompression and what constitutes "reasonable delay" before operation in mechanical small bowel obstruction. Strangulation of obstructed bowel has been attributed to delayed decisions for operative treatment.[1,2] The incidence of postoperative complications is 5–10 times greater with strangulation than with cases of nonstrangulated obstruction.[1,3,4] It is well known that strangulation of the bowel occurs without specific signs and symptoms. Thus, many surgeons believe that all patients with mechanical intestinal obstruction should have laparotomy as soon as fluid losses have been replenished.[4–6] On the other hand, the diagnosis of "partial" bowel obstruction is based on clinical and radiographic signs that, in the opinion of most surgeons, warrants a trial of tube decompression rather than immediate operative intervention.[7,8] There are still others who believe that a trial of nonoperative tube decompression should be rendered to any patient with obstruction who does not have obvious signs of strangulation.[9–11] These diverse opinions can be attributed to the paucity of objective criteria that can reliably distinguish cases of obstruction that are likely to respond to tube

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decompression from those that require early operation. It was the purpose of this review to determine the reliability of the admission clinical signs and plain abdominal radiographs in predicting the need for operative intervention in mechanical small bowel obstruction. We also compared the effectiveness of nasogastric (NGT) with nasointestinal or long tubes (NIT) in terms of successful avoidance of operative treatment.

Clinical Material

For the 10-year period beginning January 1, 1976 through December 31, 1985, 311 consecutive patients with 342 episodes of mechanical small bowel obstruction were admitted to Robert Wood Johnson University Hospital. This review excluded patients with adynamic ileus, fecal impaction (including meconium ileus), and mesenteric vascular occlusion. Plain abdominal radiographs were taken at the time of admission in all but six patients with incarcerated hernia in whom the clinical diagnosis of complete mechanical intestinal obstruction was confirmed at operation. There were 193 cases of partial bowel obstruction and 149 cases of complete obstruction. The distinction between partial and complete mechanical obstruction was based on the radiologist's interpretation of the admission abdominal radiographs. The primary distinguishing radiographic feature between partial and complete obstruction is the presence of gas in the colon above the peritoneal reflection. Cases of complete obstruction were characterized by dilated loops of small bowel with fluid levels and no visible gas in the colon, whereas cases of partial obstruction showed clear-cut evidence of colonic gas in addition to dilated loops of small bowel (Fig. 1).

The frequency of the presenting clinical symptoms is shown in Table 1. Nausea, vomiting, and abdominal pain were reported in 99% of the 342 episodes of obstruction. Abdominal pain was typically colicky in nature. Patients who denied either pain or vomiting had plain abdominal radiographs that showed dilated small bowel loops with fluid levels. Sixty-one per cent of patients in whom the duration of obstipation was documented denied passage of stool or flatus for more than 24 hours. Seven patients had obvious peritonitis, six of whom had hypotension and a temperature ≥ 100 F at the time of admission. Other admission criteria that were assessed included the presence of abdominal tenderness and leukocyte count. Neither of these correlated with the need for operation. Table 2 shows the etiology of obstruction. Adhesions from previous abdominal operations was the most common cause of obstruction, accounting for 59% of cases of complete obstruction and 73% of cases of partial obstruction. Intra-abdominal malignancy was the second most common case of obstruction, accounting for 17% of cases of complete obstruction and 10% of cases of partial obstruction. Hernia and Crohn's disease were the third and fourth most frequent causes, respectively. The correct admission diagnosis of small bowel obstruction, partial or complete, was made in 322 cases (94%). The admission diagnoses for the remaining 20 cases are shown in Table 3.

NIT were used in 64 cases of partial obstruction and 81 cases of complete obstruction, whereas NGT were used in 116 cases of partial obstruction and 68 cases of complete obstruction. Generally, the attending surgeon decided whether a long or short tube would be used, although occasionally the surgical house staff made this decision. The suspected etiology of obstruction did not

TABLE 1. *Presenting Clinical Features*

Features	No. of Cases (%)
Nausea/vomiting	340 (99)
Abdominal pain	339 (99)
Obstipation ≥24 hours	102* (61)*
Peritonitis	7 (2)
Fever ≥100 F	7 (2)
Hypotension ≤90 mmHg systolic	6 (2)

* The duration of obstipation was clearly documented in 102 cases of which 61% had obstipation ≥ 24 hours.

TABLE 2. *Etiology of Obstruction*

	PSBO	CSBO
Adhesions	140	88
Malignancy	18	25
Hernia	—	22
Crohn's	12	2
Other*	23	12

* Other causes of obstruction included gallstone ileus (4), volvulus (4), intussusception (4), abdominal abscess (4), bezoar (2), diverticulitis (2), and cause undetermined (10). Twelve cases of early postoperative obstruction were included in the adhesion group.

TABLE 3. *Incorrect Admission Diagnoses and Outcome**

	Radiographic Diagnosis	
Admission diagnosis	PSBO	CSBO
Abdominal pain	10 (7)	—
Pancreatitis	3 (2)	1 (1)
Pelvic inflammatory disease	3 (1)	—
Acute cholecystitis	2 (0)	—
Pneumonia	1 (0)	—

* Abdominal pain of uncertain etiology was the most frequent "incorrect" diagnosis. Numbers in parentheses are the number of patients who required operation, 11 of 20 (55%) in all. The admission radiographs were consistent with partial obstruction in 19 of these 20 patients.

TABLE 4. *NGT* Versus *NIT and Outcome**

	NGT	NIT	
Need for operation	80/184	83/145	
Operation ≤24 hours	52/80	12/83	($p < 0.001$)†
Postoperative complications	16/80	29/83	($p \leq 0.04$)†
Duration of postoperative ileus (days)	4.1	7.0	($p < 0.001$)†
Length of hospitalization (days)	12.2	21.0	($p < 0.001$)†

* The type of tube used for decompression did not impact on need for operative intervention. However, a significantly greater number of patients managed with NGT compared with NIT had operation within the first 24 hours of hospitalization. The incidence of postoperative ileus and length of hospitalization were significantly greater in patients managed with long tubes.

† Statistics computed by Fisher's exact test.

influence the selection of one type of tube over the other. The type of tube used also did not influence requirement for operative intervention. Thirty-eight of 193 (19%) cases of partial obstruction required operation, including 20 of 116 (10%) treated with nasogastric tubes and 18 of 64 (28%) treated with long tubes. One hundred twenty-five of 149 cases (84%) of complete obstruction required operation, including 60 of 68 (89%) treated with nasogastric tubes and 65 of 81 (80%) treated with long tubes. Tube decompression was not used in the 13 remaining cases. Long tubes passed through the pylorus in 50 of the 83 cases (60%) that required operation compared with 49 of the 64 cases (76%) treated with long tubes that did not require operative intervention ($p = 0.15$ by chi-square test). The use of nasogastric tubes *versus* long tubes was correlated with the following outcome variables: need for operation, timing of operative intervention, number of postoperative complications, duration of postoperative ileus, and length of hospitalization. These data are shown in Table 4.

One hundred eighteen of 191 patients (62%) who were managed for at least 24 hours by tube decompression showed signs of clinical or radiographic improvement within the first 24 hours of treatment. Only eight patients (5%) whose obstructions ultimately resolved without operation did not show signs of improvement during the first 48 hours of tube decompression. Improvement was recognized radiographically as decrease gaseous distention of the small bowel and clinically b spontaneous passage of stool and/or flatus. Thirty-eigh of these 191 patients (20%) did not respond to tub decompression and eventually had operation.

TABLE 5. *Timing of Operation* Versus *Postoperative Complications**

Complication	<24 Hours (N = 64)	>24 Hours (N = 99)
Wound infection	1	13
Pneumonia	1	6
Fistula/abscess	—	6
Myocardial infarction	—	1
Pulmonary embolus	—	1
Death	4	12
Total	6	39

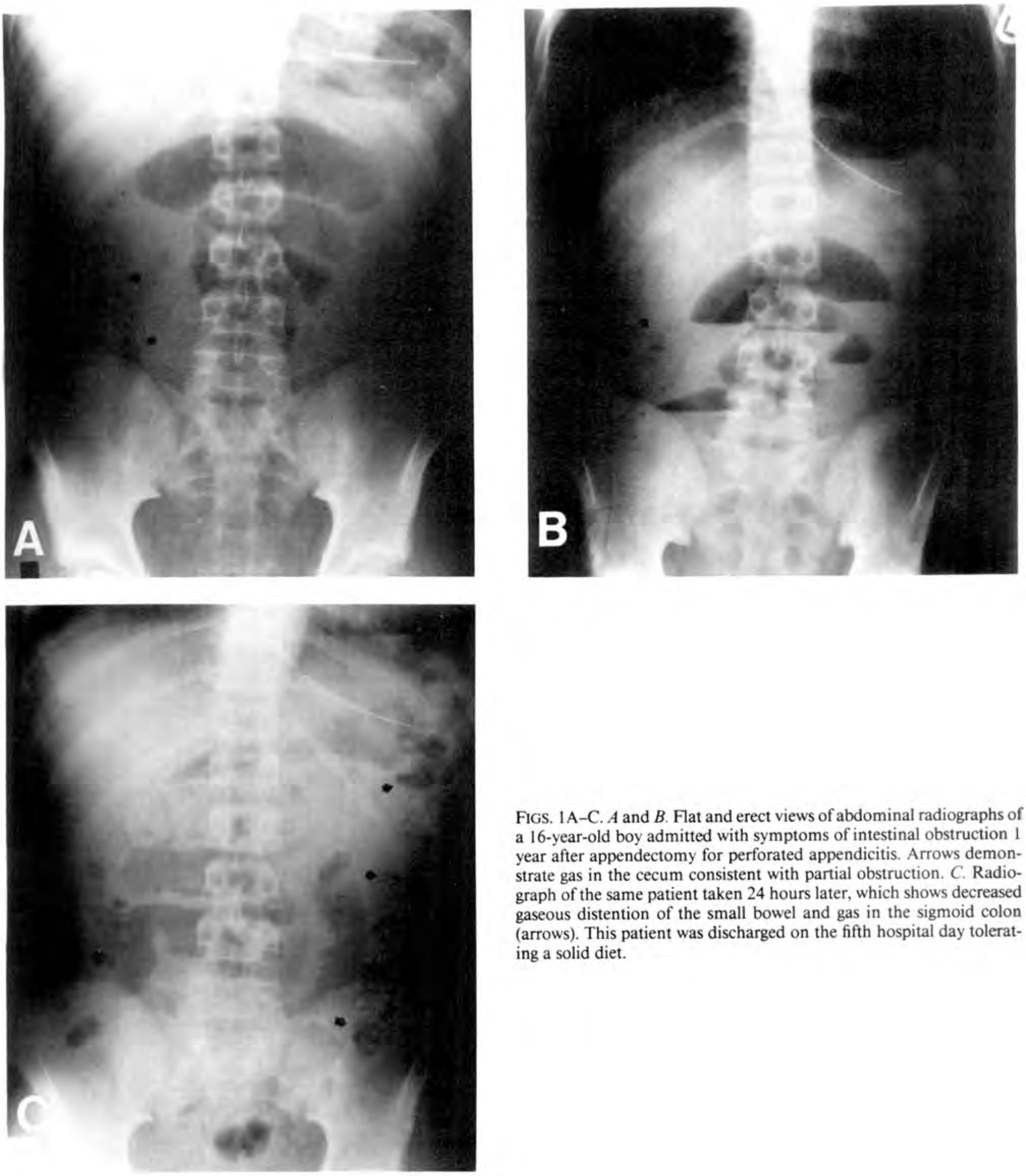
* Infectious complications were significantly more common in patients operated on more than 24 hours after admission. Fistulae and abscesses occurred in patients with either strangulation or iatrogenic perforation of the bowel.

Table 5 shows the correlation between timing of operative intervention and the frequency of postoperativ complications. Of the 64 patients who had operatio within 24 hours of admission, postoperative complications developed in six patients (9%) compared with in 3 of 99 patients (39%) who had operation more than 2 hours after admission ($p \leq 0.001$ by chi-square test Twenty-four of the 311 patients died (7.7%). Twenty-si patients had strangulation obstruction at operation Nine of these 26 patients had operation within 24 hour of admission with three subsequent deaths compare with six deaths among the 17 patients who had operation more than 24 hours after admission. Eight patient other than those with strangulation died after operation Seven of these patients had advanced carcinomatosi and one died of a massive stroke. The remaining seven patients who died did not have operation. Three of these patients were moribund with septic shock at the time o admission and four had inoperable abdominal malignancies.

Barium upper gastrointestinal (UGI) contrast studie were performed in 57 patients to establish the presence of mechanical obstruction. In 34 of the 57 patients the contrast study disclosed mechanical obstruction, and each of these patients required operative intervention In the remaining 23 patients no obstruction was demonstrated and all of these patients recovered without having operation. Those patients who required operation demonstrated either a discrete point of blockage (Fig 2B) or failure of the barium to reach the cecum after 18–24 hours (Fig. 3). In the 23 patients who did no require operation all or nearly all of the barium had entered the cecum within the 24-hour observation period.

Discussion

There is surprisingly little information in the surgical literature regarding the reliability of either clinical o radiographic criteria in predicting the need for operativ intervention in patients with intestinal obstruction Table 6 shows data from six reports on small bowe obstruction published during the past 30 years. The reports of Wolfson et al. and Hofstetter were restricted t patients with adhesive obstruction, whereas the remainder included all well-documented cases of me



FIGS. 1A–C. *A* and *B*. Flat and erect views of abdominal radiographs of a 16-year-old boy admitted with symptoms of intestinal obstruction 1 year after appendectomy for perforated appendicitis. Arrows demonstrate gas in the cecum consistent with partial obstruction. *C*. Radiograph of the same patient taken 24 hours later, which shows decreased gaseous distention of the small bowel and gas in the sigmoid colon (arrows). This patient was discharged on the fifth hospital day tolerating a solid diet.

chanical small bowel obstruction.[2,4,8,10–12] Becker, Hofstetter, Wolfson et al., and Stewardson et al. distinguished partial from complete obstruction, although Stewardson et al. excluded cases of partial obstruction from their review. Of note are the variable percentages of patients who required operation *versus* those who responded to tube decompression and avoided operative treatment. Becker and Silen et al. strongly advocated early operation for all cases of small bowel obstruction citing the abuse of tube decompression as a primary cause of death. On the other hand, Stewardson et al., Bizer et al., and Wolfson et al. recommend trials of

TABLE 6. *Small Bowel Obstruction: Previous Clinical Reports**

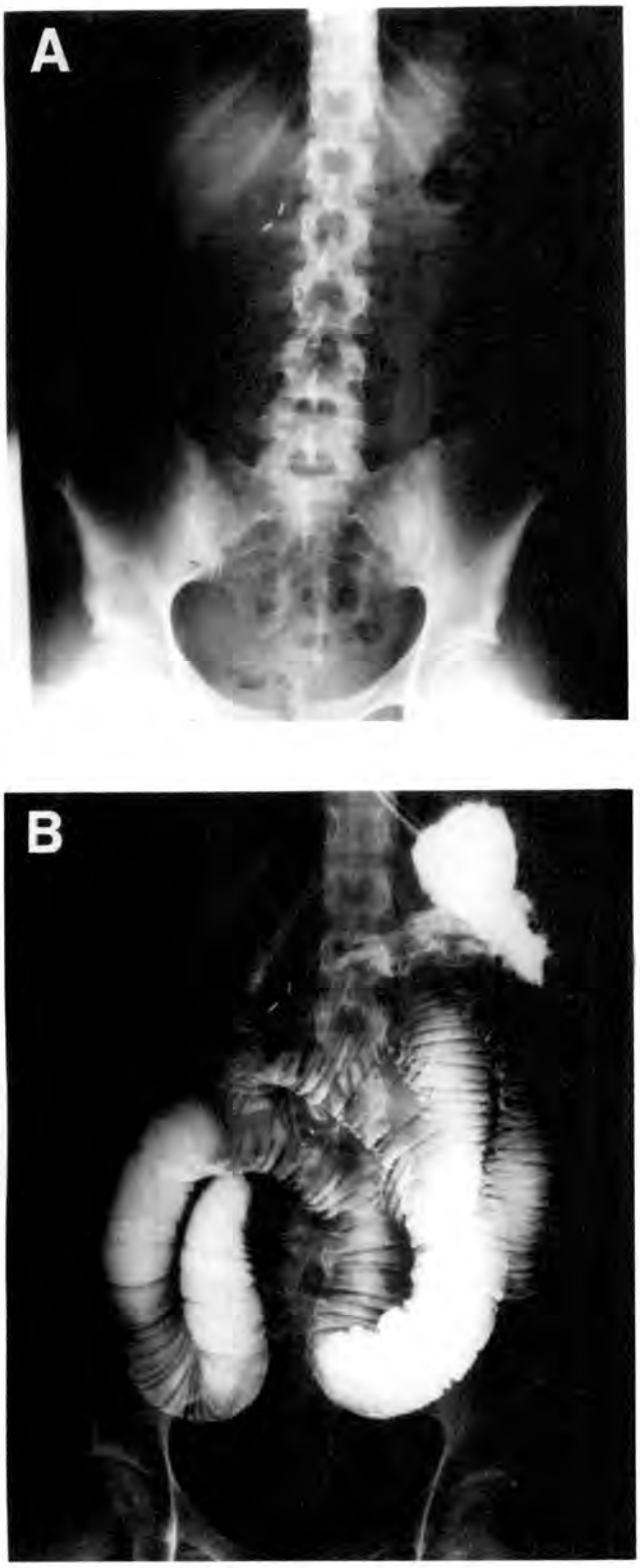
	Total Patients	No. of Patients Operated On (%)	% with Strangulation	% Total Mortality
Becker[2]	412	297 (72)	22%	12%
Silen et al.[4]	480	316 (66)	23%	11%
Stewardson et al.[10]	238	112 (47)	11%	5.5%
Hofstetter[11]	52	31 (60)	8%	1.9%
Bizer et al.[8]	405	267 (66)	10%	6.7%
Wolfson et al.[12]	127	48 (38)	12%	1.5%
Brolin (current series)	311	163 (53)	9%	7.7%

* The percentage of patients with mechanical small bowel obstruction who had operation ranged from a low of 38% (Wolfson et al.) to a high of 72% (Becker). The two series with the lowest mortality (Hofstetter, Wolfson et al.) included only patients with adhesive obstruction.

nonoperative tube decompression for all patients who lack the typical signs of intestinal strangulation. Hofstetter stated that the duration of nonoperative tube decompression should not exceed 24 hours. The overall incidence of operative intervention appears to have decreased during the past 2 decades. Table 6 also shows the incidence of strangulation and overall mortality in these clinical reports. The chronology of these reports shows a decreased incidence of both strangulation and mortality despite more conservative recommendations in treatment. In the current series the incidence of strangulation and mortality was 9% and 7.7%, respectively. These data suggest that factors other than early operative intervention are responsible for the decreased incidence of strangulation and mortality during the past 30 years.

The primary radiographic criterion for diagnosis of partial small bowel obstruction is gas in the colon above the peritoneal reflection.[6,13] The presence of colonic gas above the peritoneal reflection suggests that some air has passed beyond the obstruction, hence the blockage is incomplete. Because gas can be introduced into the rectum by digital examination, air in the rectum alone is not sufficient for making the diagnosis of partial obstruction. The radiographic diagnosis of "partial" bowel obstruction probably encompasses a number of cases of early complete obstruction, which may also show gas in the colon on the admission abdominal radiographs. In these early cases, the colonic gas antedates the time of obstruction and has not yet been evacuated. The typical radiographic features of mechanical intestinal obstruction may be absent in cases of high jejunal obstruction. Figure 2 shows the plain abdominal radiograph and subsequent barium UGI contrast study of a patient with complete obstruction 60 cm below the ligament of Treitz. The plain x-rays showed a paucity of gas in the small and large bowel without air fluid levels on the erect view. Plain radiographs performed 18 hours later showed one visible loop of small bowel. The barium UGI was performed to rule out obstruction of the proximal small bowel. In this series, barium UGI contrast studies were extremely reliable in determining need for operation. All patients whose barium studies demonstrated either a discrete site of blockage or failure of barium to reach the cecum within a 24-hour observation period ultimately required operation. Patients who recovered with tube decompression had contrast studies that showed complete transit of barium and no evidence of obstruction. Despite their great accuracy, the use of barium UGI studies should probably be limited to cases in which the diagnosis of mechanical obstruction is in doubt. Patients admitted to the hospital with partial obstruction who have not responded to tube decompression after 48 hours should be operated on without a UGI contrast study. On the other hand, patients responding to tube decompression who have no past history of abdominal surgery should have a predischarge UGI examination to rule out malignancy as a possible cause of obstruction. Barium UGI studies are probably most useful in distinguishing cases of early postoperative obstruction from prolonged adynamic ileus.

In this report, the selection of a nasogastric or long tube was made arbitrarily at the time of admission. Although some surgeons have strong sentiments for use of one type of tube over the other, there are no data demonstrating superiority of long *versus* short tubes in the treatment of mechanical intestinal obstruction. Wolfson and associates recently touted the efficacy of long tube decompression in the treatment of adhesive obstruction.[12] They made these claims despite the fact that approximately two thirds of their patients with complete obstruction did not respond to tube decompression and required operation. They also stated that passage of a long tube beyond the pylorus was of "significant predictive value" with respect to avoiding operative treatment, although no statistical support for those claims was provided. In the current review there was no correlation between need for operative intervention and whether or not long tubes passed beyond the pylorus. Fifty of the 83 patients (60%) managed with long tubes who required operation had passage of their tube into the upper small



FIGS. 2A and B. *A*. The erect admission radiograph of a 26-year-old woman who had symptoms of small bowel obstruction 2 years after laparotomy for blunt trauma. There is little gas in either the small or large bowel. *B*. A barium contrast study performed 24 hours later, which showed a discrete point of obstruction in the right midabdomen. Several hours later this patient had laparotomy and lysis of a single adhesive band.

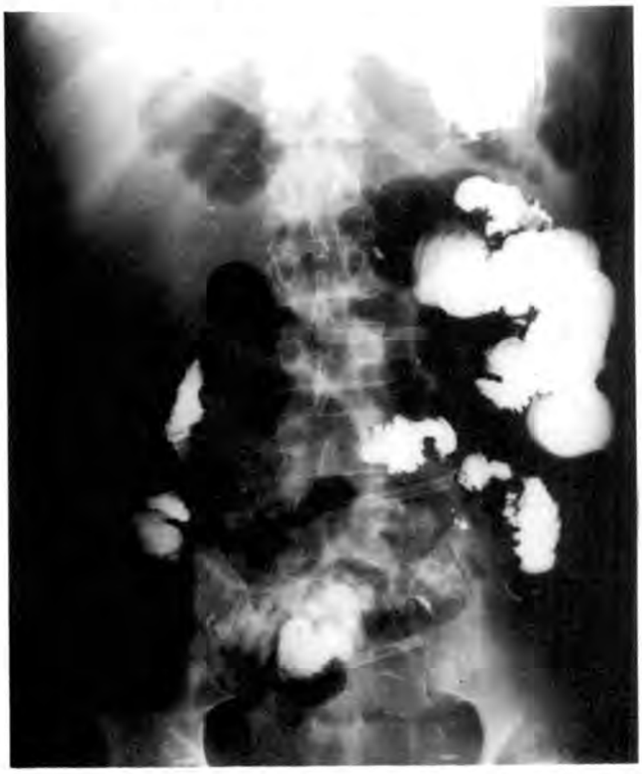


FIG. 3. Twenty-four hour delayed film of barium UGI performed on a 42-year-old man in whom signs of obstruction developed 6 days after right hemicolectomy and ileostomy for perforated cecal volvulus. The contrast study was performed after 4 days of nasointestinal tube (NIT) decompression. (Tube was removed during study). Although some barium emptied through the ileostomy, much remained in the upper small bowel. This patient had lysis of multiple adhesions on the eleventh postoperative day and had a subsequently uneventful recovery.

bowel. There was also no difference between nasogastric and nasointestinal tubes with respect to avoiding operative intervention. In this review there were several negative features associated with the use of long tubes compared with nasogastric tubes. Long tubes were associated with a significantly greater number of postoperative complications and significantly longer duration of both postoperative ileus and hospitalization (Table 3). These negative findings were most likely due to the significantly greater delay in operative intervention in patients managed with long tubes compared with nasogastric tubes. All of these data clearly show that the mere passage of a long tube into the upper small bowel does not justify delay in operative intervention.

Surgeons who favor a nonoperative trial of tube decompression for all cases of obstruction except those with signs of strangulation base support for their position on the substantial percentage of cases that resolve with tube decompression alone. Wolfson and associates operated on only 38% of 127 patients with adhesive obstruction after an empirical trial of tube decompression.[12] The incidence of postoperative complications was 30% in their report, including a 4.8% operative mortality rate and a 12% incidence of strangulation. These results are comparable to those reported by surgeons who favor early operative intervention.[4,9,10] It seems obvious that a rigid attitude favoring either an empirical trial of tube decompression on one hand or immediate operative intervention on the other will do disservice to a substantial number of patients with small bowel obstruction. It was the primary purpose of this review to determine the reliability of admission clinical and radiographic criteria in predicting the need for operative treatment. The actual decision for operative intervention was based on the clinical judgement of the attending surgeon. At our institution there is no consensus of opinion among surgeons regarding the appropriate timing of operation for small bowel obstruction. Hence, the radiographic diagnosis of partial bowel obstruction did not always result in a nonoperative trial of tube decompression and, by the same token, a number of patients with complete obstruction had prolonged treatment by tube decompression. Nonetheless, in accordance with the axiom that all cases of partial obstruction will resolve with tube decompression and all cases of complete obstruction will require operation, the admission abdominal radiographs predicted the clinical course in 82% of cases in this series. Duration of obstipation was less reliable in predicting need for operation as 31% of patients with obstipation $\leq$ 24 hours required operation, whereas 38% with obstipation for more than 24 hours were successfully treated by tube decompression. On the basis of these data we recommend that all patients with radiographic features of complete obstruction have operation as soon as fluid losses have been replaced, whereas patients with features of partial obstruction and no clinical signs of strangulation be given a trial of tube decompression with the reasonable likelihood of avoiding operation. Although 16% of patients with complete obstruction successfully avoided operation, we could not identify specific features that distinguished those patients from the 84% who required operation.

There are several causes of obstruction that generally warrant an empirical trial of tube decompression. These include Crohn's enteritis, advanced abdominal carcinomatosis, and early postoperative obstruction. Obstruction due to Crohn's disease usually resolves after 24–48 hours of treatment with parenteral steroids and antibiotics. This treatment regimen was successful in avoiding operation in 11 of the 14 cases of obstruction caused by Crohn's enteritis in this report. Patients with obstruction secondary to abdominal tumor metastasis represent a treatment dilemma because of their generally debilitated condition on one hand and the low probability of response to tube decompression on the other. Furthermore, operative treatment is frequently difficult because of blockage by tumors at multiple sites along the bowel. In this series the hospital mortality rate of obstruction due to metastatic disease was 64%. Intestinal obstruction in the early postoperative period frequently resolves with tube decompression.[14–16] With early postoperative obstruction, many surgeons prefer a long tube to a nasogastric tube because of the theoretical advantage of internal enterolysis as it passes distally through the bowel. In the early postoperative period mechanical obstruction must be distinguished from prolonged ileus. Patients who do not improve after 48 hours of tube decompression should have a barium UGI contrast study. In this review, barium contrast studies were highly reliable in determining need for operative intervention. The relatively high mortality associated with early postoperative obstruction has been attributed to unnecessary delay before re-exploration in two previous reports.[14,15] Patients who have had multiple hospital admissions and operations for adhesive obstruction probably present the greatest dilemma in terms of appropriate timing of operative intervention. At the outset, these patients are usually treated by tube decompression with the hope of avoiding another operation. During this 10-year review there were 25 such patients admitted an average of 2.64 times per patient with a mean interval of 1.8 months between admissions. All but four of these patients ultimately required operation, and none of the surviving patients have been readmitted with obstruction during the subsequent follow-up period. We therefore recommend that patients who have had more than two hospital admissions for obstruction during a 6-month interval have laparotomy.

That delayed operative intervention in this review was associated with a significantly greater number of postoperative complications supports the frequently quoted adage, "The sun should never be allowed to set (or rise) on a case of mechanical intestinal obstruction." Those who espouse this philosophy cite that there is no reliable method of distinguishing simple from strangulated obstruction.[4,6,9,17] In this review there was no correlation between the timing of operation and mortality from strangulation obstruction. However, complications other than strangulation were significantly more common among patients operated on more than 24 hours after admission (Table 4). These complications occurred almost exclusively in patients whose admission radiographs showed complete as opposed to partial obstruction. The only postoperative complications that occurred in patients admitted with partial obstruction were three wound infections and one anastomotic leak after bowel resection for strangulation. The wound infections occurred in elderly patients who were operated on at a mean 7.3 days after admission. These data suggest that increased complications other than strangulation represent the most cogent mitigating factor favoring early operation for complete small bowel obstruction.

An incorrect admitting diagnosis was made in only 20 of the 342 cases (6%) in this series (Table 3). Inaccurate diagnosis delayed operation more than 24 hours in all of the misdiagnosed patients who required operative intervention. One patient with radiographic features of complete obstruction had strangulation after a misdiagnosis of acute pancreatitis. There were also two cases of strangulated volvulus that were misdiagnosed as partial obstruction. Progression of radiographic signs led to operation within 24-36 hours in both cases, and both patients survived. These misdiagnosed volvulus cases were the only cases of strangulation in the 193 episodes of "partial" small bowel obstruction.

In summary, the requirement for operative intervention is the most critical decision to be made during the initial evaluation of patients with intestinal obstruction. In this review the radiographic distinction between partial and complete obstruction was the most reliable determinant of need for operative treatment in that 84% of patients with complete obstruction required operation compared with only 19% of patients with partial obstruction. Operations delayed more than 24 hours after admission were associated with a significantly greater number of complications. Ninety-one per cent of the postoperative complications occurred in patients with complete obstruction. On the basis of these data, we recommend that all patients with features of complete obstruction have operation shortly after admission, whereas patients with partial obstruction be given a trial of tube decompression with the likelihood of avoiding operative treatment. Nearly 75% of patients initially managed by tube decompression who ultimately avoided operation showed clinical or radiographic signs of improvement during the first 24 hours, whereas only 5% of patients whose obstructions resolved without operation did not show improvement within the first 48 hours of treatment. We therefore recommend that trials of nonoperative tube decompression for partial obstruction not exceed 48 hours. Clinical deterioration or increased small bowel distention on abdominal radiographs during the course of tube decompression warrants prompt operative intervention.

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A Prospective, Randomized Trial of Abdominal Wound Drainage in Gastric Bypass Surgery

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A prospective, randomized trial was conducted in 194 morbidly obese patients who had gastric bypass to determine the effect of subcutaneous closed suction drainage on wound infection rates. There was no difference in the incidence of postoperative wound infection with the use of drains compared with simple abdominal closure. Organisms isolated from infected wounds were predominantly skin flora and did not differ between the two groups. Patients with wound infections had significantly prolonged hospitalizations compared with those without infections, but in the subgroup with wound infections there was no difference in hospitalization time between the drainage or control groups.

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OBESE PATIENTS who have abdominal surgery are at increased risk for development of postoperative wound infections.[1,2] Both prolonged operating time and the development of hematomas, seromas, or dead space in the subcutaneous tissue are believed to predispose to wound infection.[1,3] The theoretical advantage of wound drainage, with removal of blood and serum and the obliteration of dead space, would thus seem to make the routine use of subcutaneous drains in abdominal closure in the obese patient particularly attractive. Several retrospective, nonrandomized reports in both the general surgical[4,5] and gynecologic[6,7] literature support this contention. However, few controlled, randomized trials specifically address the question of abdominal wound drainage in clean or clean-contaminated cases.

We report the results of a prospective, randomized trial of prophylactic closed suction drainage of the subcutaneous tissue in 194 patients who had gastric bypass.

Materials and Methods

All patients who had gastric bypass at our institution between June 1982 and August 1986, were included in the study. All patients received identical pre- and postoperative care according to a written protocol. Patients were admitted 1 or 2 days before surgery. They received a hexachlorophene abdominal scrub 3 times per day before surgery and a hexachlorophene shower and shampoo the evening before surgery. Patients not allergic to penicillin received cefazolin, 1 g intravenously, before and after operation before June 1983, after which the dose of cefazolin was doubled.[8] Patients allergic to penicillin received either vancomycin with an aminoglycoside (2 patients) or an aminoglycoside alone (4 patients). Three patients with valvular heart disease received appropriate endocarditis prophylaxis.[9] Subcutaneous heparin, 5000 units every 8 or 12 hours depending on antithrombin III level, was begun before operation and continued until discharge.[10]

In the operating room the abdomen was prepared with chlorhexidine detergent followed by povidone-iodine solution. After the skin incision, the subcutaneous tissue was separated to the fascia by lateral traction of the wound edges to minimize bleeding and tissue necrosis.[11] The fascia was divided with electrocautery. All patients had gastric bypass as previously described[12] with retrocolic Roux-en-Y gastrojejunostomy with a 10–15 mL gastric pouch created with a double row of staples and side-to-side jejunojejunostomy made using the stapler. The gastrojejunal anastomosis was performed in two layers with nonabsorbable sutures. The

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abdomen was irrigated with normal saline and the fascia closed in a single layer with interrupted, heavy nonabsorbable monofilament or synthetic absorbable suture.

Patients were then randomized into two groups. After irrigating the subcutaneous tissue with 25% povidone-iodine solution, one group had their abdominal wounds closed over a closed suction drain brought out through a separate stab incision. Wounds in the control group were closed without drains. The skin was closed with skin staples.

Drains were left to self-suction and removed when drainage was less than 30 mL/24 hours. Drains were not irrigated. Patients were discharged from the hospital when able to take one liter of fluids by mouth in a 24-hour period. Skin staples were removed approximately 2 weeks after operation at the first outpatient visit. All wounds were examined by both a surgeon and nurse practitioner with a minimum follow-up of 1 month.

Wounds were defined as infected if pus was present at the incision site. Serous drainage with negative bacterial cultures and without clinical evidence of infection were not considered wound infections. Suture sinuses were also not included in the infected group. All operations were classified as clean-contaminated.[1]

Preoperative per cent ideal body weight was calculated by dividing the preoperative weight by the mean ideal body weight for height according to Metropolitan Life Insurance Company tables (1955). Duration of operation was measured from skin incision to closure.

Results were compared using the chi-square test or Student's t test where appropriate.

Results

One hundred ninety-four morbidly obese patients had gastric bypass between June 1982 and August 1986. All patients were entered into the study. One hundred two patients were randomized to receive closed suction drains in their abdominal closure. Wounds were closed without drains in the remaining 92 patients. Thirty-day follow-up of wounds was available for all patients.

The two groups are compared in Tables 1 and 2. Risk factors previously associated with postoperative wound infection, including age, weight, preoperative hospital stay, duration of operation, additional procedures performed, diabetes mellitus, and chronic steroid use, were similar between the drainage and control groups.

There were 11 wound infections in the drainage group (10.8%) compared with 10 in the control group (10.9%). The overall rate of postoperative wound infection was 10.8% (Table 3). In addition, three patients (2 drainage, 1 control) had secondary wound infections develop after re-exploration for complications (1 anastomotic leak, 2 acute gastric dilatations). Subcutaneous drains were used in two of these three reoperations. Because these wound infections occurred after contaminated cases, they are excluded from further analysis.

There has been a decrease in the wound infection rate over the 5-year study period, from 20% in 1982 to 7.4% in 1986 (Fig. 1), although this difference is not statistically significant.

Wound cultures were available in 16 of 21 patients (8 drainage, 8 control). There was no significant difference in either the number or type of organism isolated between the two groups (Table 4). *Staphylococcus* sp. and *Streptococcus* sp. were the most common organisms isolated (76%). Six patients (2 drainage, 4 control) had more than one organism isolated. Five patients with wound infections had concomitant cholecystectomy performed at the time of gastric bypass (3 drainage, 2 control). Intraoperative bile cultures were available in

TABLE 1. *Demographic Data*

	Drainage (N = 102)	Control (N = 92)
Age (yrs)	38 ± 8	37 ± 9
Male	19	20
Female	83	72
% Preoperative ideal body weight	214 ± 36	212 ± 32
Duration of operation (min)	258 ± 64	260 ± 50
Diabetes mellitus	6	10
Chronic steroid use	1	2
Preoperative hospitalization		
1 day	18	18
2 day	70	68
≥3 days	14	6

TABLE 2. *Additional Procedures*

	Drainage (N = 102)	Control (N = 92)
No. of patients	68 (67%)	51 (55%)
No. of procedures	88	64
Liver biopsy	38	29
Cholecystectomy	20	16
Appendectomy	0	1
Bilateral tubal ligation	10	7
Ventral/umbilical herniorrhaphy	8	4
Other	12	7

TABLE 3. *Wound Infection Rates*

	No. of Patients	No. of Infections
Drain	102	11 (10.8%)
Control	92	10 (10.9%)
Total	194	21 (10.8%)

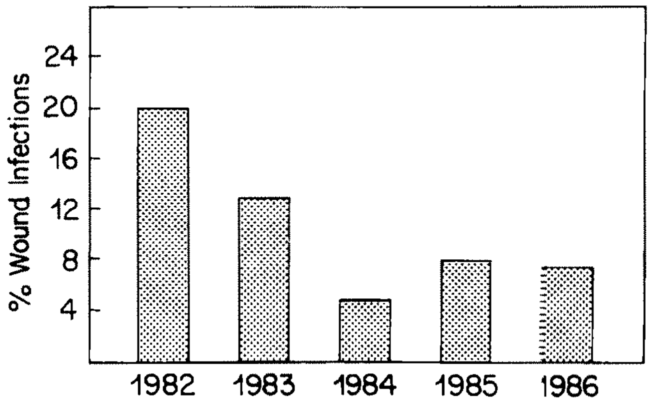

FIG. 1. Yearly wound infection rates.

three of these patients and were negative. A wound infection developed in the only patient to have incidental appendectomy and cholecystectomy. *Escherchia coli* was isolated from the appendix (bile cultures were negative), whereas wound drainage grew *Staphylococcus aureus* and *Bacteroides fragilis.*

In both the drainage and control groups, patients in whom postoperative wound infections developed had significantly longer hospital stays compared with patients without complications. The mean postoperative stay for infected *versus* noninfected patients was 17.2 ± 13.7 *versus* 8.2 ± 1.8 days ($p < 0.001$) and 12.1 ± 8.4 *versus* 8.6 ± 1.7 days ($p < 0.01$) in the drainage and control groups, respectively. Of those patients with wound infections in the two groups, there was no significant difference in either the severity of infection or the duration of postoperative stay.

Discussion

We conducted a prospective, randomized trial of closed suction drainage of abdominal wounds in 194 patients who had gastric bypass over a 5-year period at a single institution. There was no significant difference in the incidence of postoperative wound infection with the use of subcutaneous drains compared with simple abdominal closure.

TABLE 4. *Bacteriology of Infected Wounds*

Organism Isolated*	Drain	Control	Total
Coagulase (−) Staphylococcus	4	5	9 (43%)
Staphylococcus aureus	2	3	5 (24%)
Streptococcus sp.	—	2	2 (10%)
Enterobacter	2	—	2 (10%)
Bacteroides fragilis	—	1	1 (5%)
Diptheroids	1	1	2 (10%)

* More than one organism may have been isolated from a single wound infection.

The overall rate of postoperative wound infection in our study is comparable to other published reports for clean-contaminated cases[1,2] and gastric bypass procedures.[5,13–18] In a study comparing closed suction drainage with heavy nylon stay sutures to reduce wound dead space in morbidly obese patients, Kozol et al.[13] similarly found no reduction in wound infections with the use of closed suction drains.

Although both groups were comparable with respect to known risk factors for postoperative wound sepsis, the drainage group had a slightly higher number of patients with prolonged preoperative hospital stays. Of 14 patients in the drainage group hospitalized 3 or more days before surgery, wound infections developed in three patients (preoperative hospitalizations of 6, 10, and 13 days, respectively) compared with none of six patients in the control group. However, even excluding these patients, the use of subcutaneous drains did not significantly reduce the incidence of wound infections.

Several factors may account for the lack of efficacy of drains in this study. The use of subcutaneous drains in obese patients is based on the assumption that the large subcutaneous layer results in increased dead space and the accumulation of blood and serum, which in turn predispose to wound infections. However, techniques aimed at reducing the amount of bleeding and tissue trauma and necrosis, such as separating the subcutaneous fat by lateral traction and the use of electrocautery, may reduce the volume of tissue fluid accumulation and diminish the effect of drains.

Secondly, by providing a route for bacteria to get into the wound as well as out, drains may increase the risk of infection.[19–21] Although the risk is certainly less for closed suction drains than simple conduit (Penrose) drains,[22] the high percentage of skin contaminants isolated suggest that retrograde infection may still play a role.

Closed suction drains may also become obstructed with tissue fragments and fail to function properly. Although we did not routinely irrigate the drains or document patency at the time of removal, the total volume of drainage or the day of drain removal was not appreciably different between infected and noninfected wounds.

Also noteworthy is a reduction in the rate of wound infections during the course of this trial. Two factors may account for this. A preliminary review of our data revealed that increasing the perioperative dose of cefazolin in 1983 from 1 to 2 g resulted in a significant reduction in wound infections.[23] Secondly, the institution of more rigorous wound surveillance as a byproduct of this study, which has been shown by others[24,25] to lead to a reduction in wound infection rates, may have also contributed to this trend.

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Gastrointestinal Anastomoses

Factors Affecting Early Complications

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A retrospective review of gastric and colonic anastomoses during a recent 12-month period was performed at the Mayo Clinic. One hundred sixty-nine patients had gastroduodenal or gastrojejunal anastomoses (Group I). Five hundred nineteen patients had ileocolonic or ileorectal (222) and colocolonic or colorectal (297) anastomoses (Group II). Major anastomotic complication rates for Group I patients were: leaks, 1%; hemorrhage, 2%; and stenosis or obstruction, 2%. Reoperations and deaths secondary to anastomotic complications during the postoperative period were 2% and 0.6%, respectively. Corresponding rates for Group II were 2%, 1%, and 4%, with reoperative and anastomotic death rates of 1% and 0.2%, respectively. In Group I patients, length of operation had a significant effect ($p < 0.01$) on anastomotic complications. In Group II patients, a significant increase in complications was related to the presence of obstruction ($p < 0.001$), recent weight loss (>10 pounds) ($p < 0.02$), malignancy ($p < 0.04$), and sepsis ($p < 0.05$).

THE REPORTED RATES of major complications involving anastomoses of the gastrointestinal tract have varied widely, and debate has centered around the causes of these complications in regard to anastomotic leaks, in particular. To determine the rates of major complications and to determine the pre- and intraoperative factors that affect these rates we reviewed our experience with gastrointestinal anastomoses during a recent 12-month period.

Materials and Methods

Between January 1, 1982 and December 31, 1982, 688 patients had abdominal surgery at the Mayo Clinic with performance of an anastomosis involving either the stomach (gastroduodenal, gastrojejunal) or the colon (ileocolonic, ileorectal, colocolonic, or colorectal). The records of these patients were reviewed retrospectively for multiple preoperative (Table 1) and intraoperative (Table 2) variables that might affect the rate of anastomotic complications. A "major complication" was defined as leak, hemorrhage, or obstruction (stenosis). Leaks were defined by any evidence of internal or external fistula, abscess, or intra-abdominal sepsis, and they were identified either at reoperation or *via* examinations with contrast medium. Hemorrhage was defined as significant bleeding (>100 mL/h) in the immediate postoperative period that required emergency reoperation or hemodynamic resuscitation. Minor anastomotic bleeding that did not require transfusion was not included. Obstruction or stenosis was defined as narrowing, kinking, or swelling of significant magnitude to delay or halt normal passage of intestinal contents. This obstruction was defined either endoscopically or radiographically with contrast material. Gastric atony was not included in this group. The rates of minor complications (*e.g.*, wound infection, urinary tract infection, and pneumonia), reoperations, and operative mortality were also analyzed. Results were analyzed by using Fisher's exact test (two tailed), the Wilcoxon test, or Student's t-test where appropriate.

Results

Group I

One hundred sixty-nine patients (88 men and 81 women; mean age: 60 years) had either gastroduodenal or gastrojejunal anastomosis. The rates of major anastomotic complications are listed in Table 3. There were no significant differences in these rates among the various

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types of gastric anastomoses, with overall rates for leaks of 1%; hemorrhage, 2%; and stenosis/obstruction, 2%. Reoperations were required in six patients within 3 months of the initial procedure; however, only three patients had re-exploration because of anastomotic complications (2%). The operative mortality rate was 9% overall, with one death (0.6%) secondary to anastomotic complication. Tables 1 and 2 show the rates of anastomotic complications and the various preoperative and intraoperative factors. None of the preoperative factors were significant predictors of complications; however, the presence of malignancy and recent or intraoperative radiation therapy approached significance ($p = 0.07$; $p = 0.09$, respectively). No significant differences were noted when comparing age or sex of patients with or without complications.

Length of surgery was the only intraoperative variable that was significant: 247 minutes for those with anastomotic complications compared with 174 minutes for those without complications ($p < 0.02$). Patients with malignancy had an 8% rate of major complication compared with 1% for patients without malignancy ($p = 0.07$).

Group II

Five hundred nineteen patients (264 men and 255 women; mean age: 63 years) had anastomosis involving the colon or rectum (ileocolonic, ileorectal, colocolonic, colorectal). The rates of major complications were leaks, 2%; hemorrhage, 1%; and stenosis/obstruction, 4%. The reoperation rate was 2% overall (1% secondary to anastomotic complications) and the mortality rate was 3% (0.2% secondary to anastomotic complications).

TABLE 1. *Preoperative Variables and Risk of Major Complications*

	Patients, %	
	Gastric (Group I)	Colonic (Group II)
Steroids		
Yes	8	11
No	4	6
Diabetes mellitus		
Yes	7	8
No	5	6
Obstruction		
Yes	5	37*
No	5	3
Weight loss (malnutrition)		
Yes	12	15†
No	4	5
Malignancy		
Yes	8	7‡
No	1	3
Sepsis		
Yes	0	9§
No	5	5
Hypotension		
Yes	0	15
No	5	5
Radiation therapy		
Yes	18	10
No	4	5

* $p < 0.0001$, †$p < 0.02$, ‡$p < 0.04$, §$p < 0.05$.

TABLE 2. *Intraoperative Variables and Risk of Major Complications*

	Patients, %	
	Gastric (Group I)	Colonic (Group II)
Emergency		
Yes	0	12
No	5	6
Technique		
1 layer	0	15
2 layer	5	5
Stapled	6	11
Suture (2 layer)		
Chromic/silk	2	7
Silk/silk	14	0
Vicryl/silk	6	5
Other	6	8
Surgeon		
Resident	5	6
Staff	4	6
Procedure		
Gastrojejunostomy (loop)	5	
Gastroduodenostomy (Billroth I)	0	
Gastrojejunostomy (Billroth II)	2	
Gastrojejunostomy (Roux-en-Y)	12	
Ileocolostomy		4
Colocolostomy		5
Ileorectostomy		10
Colorectostomy		11
Pathology		
Cancer	8	7
Inflammatory	0	4
Ulcer	0	
Other	6	5

There were no statistically significant differences in the rates of leak (1% and 5%) or hemorrhage (1% and 0%) for anastomoses performed above or below the peritoneal reflection. However, there was a significant difference in the rates of stenosis/obstruction for intraperitoneal and extraperitoneal anastomoses (3% and 9%, $p < 0.02$). Minor complications were noted with increased frequency ($p < 0.0001$) in anastomoses involving the ileum, whereas an increased rate of reoperations ($p = 0.02$) was noted in colocolonic or colorectal anastomoses. No differences were noted when comparing age or sex of patients with or without anastomotic complications.

Several preoperative variables were associated with an increased risk of anastomotic complication (Table 1). Obstruction of the colon (37% and 3%, $p < 0.0001$), recent weight loss of greater than 10 pounds (malnutri-

TABLE 3. *Anastomotic Complications and Type of Anastomosis*

	Patients					
	Anastomotic Leak	Anastomotic Hemorrhage	Anastomotic Stenosis/ Obstruction	Minor Complications	Reoperation*	Mortality†
	% (N)	% (N)	% (N)	% (N)	% (N)	% (N)
Gastric (Group I)						
Gastrojejunostomy (73) (palliative)	0	[illegible] (2)	3 (2)	18 (13)	3 (2)	11 (8)
Gastroduodenostomy (18) (Billroth I)	0	[illegible]	0	11 (2)	0	6 (1)
Gastrojejunostomy (53) (Billroth II)	0	[illegible]	2 (1)	19 (10)	4 (2)	6 (3)
Gastrojejunostomy (25) (Roux-en-Y)	4 (1)	[illegible] (2)	0	28 (7)	8 (2)	16 (4)
Total	1	[illegible]	2	19	4	9
Colonic (Group II)						
Colocolostomy (190)	1 (2)	(2)	3 (6)	4 (7)	3 (6)	1 (2)
Ileocolostomy (212)	1 (3)	(3)	2 (4)	13‡ (28)	0§	4 (9)
Colorectostomy (107)	5 (5)	[illegible]	8‖¶ (9)	2 (2)	3 (3)	2 (2)
Ileorectostomy (10)	0	[illegible]	10¶ (1)	30# (3)	0	0
Total	2		4	8	2	3

* Reoperation for all causes (secondary to anastomotic complications, 2% in Group I and 1% in Group II).

† Deaths due to any cause (deaths secondary to anastomotic complications, 0.6% in Group I and 0.2% in Group II).

‡ Ileocolostomy higher than colocolostomy ($p < 0.001$ and colorectostomy ($p < 0.001$).

§ Ileocolostomy lower than colocolostomy ($p < 0.02$) and colorectostomy ($p < 0.04$).

‖ Colorectostomy higher than ileocolostomy ($p < 0.02$) and colocolostomy ($p < 0.05$).

¶ Colorectostomy and ileorectostomy higher than colocolostomy and ileocolostomy combined ($p < 0.02$).

# Ileorectostomy higher than colocolostomy ($p < 0.01$) and colorectostomy ($p < 0.01$).

tion) (15% and 5%, $p < 0.02$), malignancy (7% and 3%, $p < 0.04$), and sepsis (9% and 6%, $p < 0.05$) were all significant. None of the intraoperative variables (Table 2) significantly affected the rate of major anastomotic complications.

Discussion

Much discussion has appeared in the literature concerning anastomotic complications, primarily anastomotic leaks after colorectal surgery. Rates as high as 50% have been reported when routine postoperative visualization with contrast material has been performed, with corresponding clinical leak rates of 10–30% reported after low anterior resections.[1] Leak rates have been lower for intraperitoneal colonic and gastric anastomoses (8% and 5%, respectively).[2,3] In this study, leak rates were 1% for gastric and 2% for colonic anastomoses. For colonic anastomoses, there was an increased rate of anastomotic leak in patients with colorectal anastomoses (5% compared with 1%), but this was not statistically significant.

Several studies have reported various factors to be related to an increased rate of anastomotic complications: advanced age, diabetes mellitus, weight loss, emergency surgery, infection, hypotension, prolonged surgery, inexperienced surgeon, and performance of extraperitoneal anastomosis.[4–6] Our review identified preoperative bowel obstruction as the strongest predictor of anastomotic complications (37% compared with 3%, $p < 0.0001$) in colonic surgery; other predictors were significant weight loss ($p < 0.02$), presence of malignancy ($p < 0.04$), and sepsis ($p < 0.05$). No factors in gastric surgery except length of operation ($p = 0.02$) were significant.

The reports concerning the technical aspects of anastomoses have yielded conflicting data concerning anastomotic complications when comparisons were made between sewn and stapled anastomoses,[7–11] single- and double-layered sewn anastomoses,[12] and everted and inverted sewn anastomoses.[13] However, the consensus of these studies is that inverted anastomoses are superior to everted anastomoses and that no significant differences exist between single or double and sewn or stapled anastomoses, although the rate of stenosis is increased with stapled or double-layered anastomoses compared with single-layered anastomoses. In our study, the majority of anastomoses were constructed in a double layer, inverting fashion and there was no statistically significant difference when comparing stapled and sewn anastomoses. We did, however, note an increased rate of obstruction/stenosis in anastomoses performed to the rectum ($p = 0.02$).

Our study highlights that the level of anastomotic complications, particularly leaks, can be held to an acceptable level with attention to technical details regardless of whether the anastomosis is constructed with the stapler or hand-sewn, performed by a resident or a staff surgeon, or performed above or below the peritoneal reflection. The technical principles involving all anastomoses warrant repetition: (1) good blood supply, (2) no tension, (3) adequate lumen, (4) water-tight anastomosis, and (5) no distal obstruction. There is no significant effect of diabetes mellitus, steroid use, age, or sex on rates of complications, but radiation therapy and hypotension may play a role. Colonic obstruction, malignancy, weight loss/malnutrition, and sepsis all had a significant role in anastomotic complications in patients who had colonic anastomoses, and particular care should be taken when these factors are present.

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A Scientific Evaluation of Operative Choledochoscopy in Acute Cholangitis

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A prospective study to determine the safety and effectiveness of choledochoscopy in acute cholangitis and acute suppurative cholangitis due to common bile duct stones was conducted on 70 patients. Common bile duct pressures determined on the first 20 patients showed that choledochoscopy was unlikely to cause cholangiovenous reflux. Laboratory and clinical parameters revealed that choledochoscopy did not cause septicemia, worsen cholangitis, or provoke acute pancreatitis. There was no iatrogenic injury during choledochoscopy, and the choledochoscopic views were minimally affected by cholangitis. Choledochoscopy detected overlooked stones after conventional methods of exploration of common bile ducts in 14.3% of patients and it helped to remove impacted stones in 2.9% of patients. As a result, the incidence of retained stones after choledochoscopy was 1.4%. Time spent in choledochoscopy was short, and the total postoperative septic complication rate was only 10%. There was no operative mortality. It is concluded that choledochoscopy is safe and effective in cholangitis.

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OPERATIVE CHOLEDOCHOSCOPY in elective common bile duct surgery is widely accepted because of its value and safety.[1–14] By direct inspection through the choledochoscope, the risk of retained common bile duct stones is reduced and latent pathologic lesions and anatomic abnormalities are discovered. Furthermore, through the operative channel, biopsy of mucosal lesions and removal of impacted stones can be performed.[14,15]

The place of choledochoscopy in acute cholangitis is less well defined as biliary tract infection makes the procedure potentially more dangerous. Continuous irrigation under pressure is required in choledochoscopy to maintain distension of the ductal system and to clear bile and debris to allow good vision. Cholangiovenous reflux of infected bile occurs if the common bile duct pressure is high, resulting in bacteremia, endotoxemia, and septicemia.[16,17] Similarly, reflux of infected bile under pressure up the biliary system may worsen cholangitis, and reflux into the pancreatic duct may cause acute pancreatitis.[2,18] Leakage of irrigant around the choledochoscopes is inevitable and may give rise to increased incidences of postoperative intraperitoneal and wound sepsis. Furthermore, the infected biliary tree may be more prone to iatrogenic injury as there is tissue congestion, hyperemia, and increased tissue friability. On the other hand, choledochoscopic views may be worse in cholangitis because of the presence of turbid infected bile, tissue edema, tissue congestion, and inflammatory webs resulting in a higher incidence of retained common bile duct stones.

In deciding whether choledochoscopy should be performed in acute cholangitis, the increased risks of surgical complications have to be balanced against the benefits. Because there is no such information in the medical literature, we decided to determine this scientifically.

Materials and Methods

A prospective study was conducted on 70 consecutive patients with emergency operations done for cholangitis or acute suppurative cholangitis[19,20] with common bile duct stones. During the study, 10 patients who had emergency exploration of common bile ducts for stones were excluded because of: (1) intrahepatic stones (3 patients). Choledochoscopy is valueless for these stones because they are beyond the reach of the instrument, (2) acute obstructive suppurative cholangitis[19,20] with pro-

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found septicemic shock (5 patients), and (3) serious associated medical diseases, including heart failure (1 patient) and chronic renal failure (1 patient). In the last two groups of patients, we considered it unethical to prolong the operation time and to introduce unknown additional surgical risks by performing choledochoscopy. Three of these patients died soon after operation.

The indication for emergency surgery were: (1) unrelenting cholangitis with high swinging fever and severe abdominal signs (26 patients), (2) failure to respond to conservative treatment (13 patients), (3) cholangitis with septicemia (6 patients), (4) impending septicemic shock with rising pulse and falling blood pressure (16 patients), and (5) transient septicemic shock that responded to preoperative resuscitation (9 patients). These 70 patients who had emergency operations represented 14.2% of all patients treated for cholangitis during the study. The majority of patients responded to conservative treatment with nasogastric aspiration, intravenous fluid, and systemic antibiotics.

All patients received 2 g of cefamandole and 2 mg/kg of gentamicin intravenously before operation. Cholecystectomy was done if the gall bladder was not removed in a previous operation. The duodenum and the head of the pancreas were mobilized by the Kocker maneuver. The common bile duct was opened through a longitudinal supraduodenal incision between two stay stitches after bile was aspirated for aerobic and anaerobic cultures. The duct was thoroughly flushed, Bakes' dilators were passed through the sphincter of Oddi into the duodenum, and Desjardins forceps and Fogarty catheters were passed up and down the duct until the surgeon was satisfied that the duct was clear of stones.

On completion of routine ductal exploration, choledochoscopy was performed with the stay stitches crossed over the rigid Storz choledochoscope (Karl Storz GmbH & Co., Tuttlingen, West Germany). The irrigating fluid was warm normal saline in plastic container placed within a pressure cuff inflated to 300 mmHg suspended 1 m above the patient. If retained stones were detected, they were removed and choledochoscopy repeated until the duct was clear. The common bile duct was then closed around a T-tube. A postexploratory operative T-tube cholangiogram was done before the abdominal wound was closed.

Several additional investigatory procedures were performed on the 70 patients under study.

Common Bile Duct Pressures

A French 5 polyethylene catheter was inserted into the instrument channel of the choledochoscope with the tip protruded for 1 cm beyond the instrument. Side holes were cut in the protruding part of the catheter, which was connected through a three-way stopcock to a water manometer. The choledochoscope was introduced into the common bile duct with the end pointing towards the liver. The zero mark of the manometer was placed at the level of the common bile duct. The stay stitches were crossed to reduce the leak of saline around the instrument. The irrigating fluid was delivered with the pressure cuff completely deflated. The water manometer was filled with normal saline to a height of 60 cm and then opened to the common duct catheter. The common bile duct pressure, that is, the pressure to which the saline column settled, was then recorded. The measurement was repeated twice. The cuff pressure was inflated at steps of 50 mmHg until the cuff pressure reached 300 mmHg. At each pressure increment, the common duct pressure was measured twice. Care was taken to keep the catheter in the center of the common bile duct during measurement of common duct pressure by checking through the choledochoscope. The cuff pressure was then deflated at steps of 50 mmHg until the cuff was completely deflated, and common duct pressure was again measured twice at each pressure decrement. The average of the four values taken at each variation in cuff pressure was taken as the common bile duct pressure.

As this common bile duct pressure measurement was troublesome and time consuming, and the common duct pressures were consistent, we performed it only on the first 20 consecutive patients in this study.

Septicemia

Blood for aerobic and anaerobic cultures were taken routinely before operation and after choledochoscopy. Blood cultures were also taken whenever the patients had chills, rigors, or fever over 39.5 C.

Persistent Cholangitis

The duration of postoperative pyrexia and hospital stay were recorded. Liver function tests were routinely checked before and after operation at intervals of every 3 days.

Bile Cultures

Routine aerobic and anaerobic cultures were taken for gall bladder bile (in patients with intact gall bladders) and common bile duct bile. All culture specimens were sent to the laboratory for plating and culture as soon as possible.

Acute Pancreatitis

Serum amylase levels were determined before operation and after choledochoscopy. A raised serum amylase level of over 7 times the upper limit of normal was taken as diagnostic of acute pancreatitis.

Choledochoscopic Views

After operation, the surgeon filled out a special form giving details on choledochoscopic views. Particular attention was given to assess whether the choledochoscopic examination was complete and whether the duodenal mucosa, the common bile duct, the bifurcation, and the right and the left hepatic ducts were clearly seen. Finally, the surgeon was asked to give his subjective assessment as whether cholangitis affected the choledochoscopic views.

Iatrogenic Injury to the Biliary Tree

Any inadvertent injury to the biliary tree during choledochoscopy, however minor, was recorded.

Value of Choledochoscopy

Choledochoscopy was considered valuable whenever it detected overlooked common bile duct stones left after exploration of common bile duct and whenever it was used in the removal of impacted stones that were not taken out by the conventional methods.

Time Spent in Choledochoscopy

The exact time spent in choledochoscopy was measured and recorded. This did not include time taken to remove impacted stones.

Incidence of Retained Common Bile Duct Stones after Choledochoscopy

Choledochoscopy was considered a failure whenever retained common bile duct stones were detected on postexploratory operative cholangiograms after choledochoscopy or on T-tube cholangiograms performed on the second postoperative week.

Wound and Intraperitoneal Sepsis

All patients with suspected wound or intraperitoneal sepsis were inspected by one assessor. All patients were followed up at 2 and 6 weeks after discharge from hospital and then at 3-month intervals in a specific outpatients clinic. They were contacted by telephone to attend the clinic when they did not turn up. Aerobic and anaerobic cultures were taken for patients with infected wounds. The criteria of Ljungqvist,[21] based on the clinical appearance of the wounds combined with the results of cultures, was used to determine whether the wounds were infected or clean. Wounds with purulent discharge and wounds with serous discharge that gave positive bacteriologic culture were classified as infected. Patients with wounds with serous discharge after they had returned home and, therefore, cultures could not be taken were also included in the infected group.

Operative Mortality

Any patients who died within that hospital admission with emergency operation performed for cholangitis is considered as operative mortality.

Results

We prospectively studied 70 patients with acute cholangitis and acute suppurative cholangitis.[19,20] There were 34 men and 36 women. The ages ranged from 33 to 89 years. The mean age ± SD was 65.8 ± 12.2 years. Forty-seven patients had recurrent pyogenic cholangitis,[22] whereas 23 patients had gall stones in common bile ducts. Sixty-one patients had no previous biliary tract operations, six patients had one each, two patients had two each, and one patient had three.

Common Bile Duct Pressures

The common bile duct pressures (mean ± SD) at cuff pressures of 0, 50, 100, 150, 200, 250, and 300 mmHg were 2.2 ± 0.4, 4.3 ± 1.7, 5.6 ± 1.6, 7.4 ± 2.1, 8.6 ± 2.3, 9.8 ± 2.9, and 13.1 ± 3.9 cm H_2O, respectively.

Even with irrigant delivered at high cuff pressures, the common bile duct pressures never exceeded the safety limit of 25 cm H_2O recommended by Dellinger and his associates.[16] As cholangiovenous reflux only occurs in men at common duct pressure of 30 cm H_2O and above,[16,17] common duct pressure measurement showed choledochoscopy in acute cholangitis and acute suppurative cholangitis to be safe.

Septicemia

Preoperative blood culture was positive for aerobes in 31 patients (44.3%). There was no anaerobes isolated. The most common organisms isolated were *Escherichia coli* (24 patients), *Klebsiella* sp. (2 patients) and *Streptococcus faecalis* (2 patients).

Postcholedochoscopy blood culture was positive for aerobes in 10 patients (14.3%). Again, no anaerobes were isolated. All patients with positive postcholedochoscopy blood cultures had positive preoperative blood cultures, and the organisms isolated were the same. These suggest that the positive postcholedochoscopy blood culture was the result of cholangitis rather than cholangiovenous reflux of infected bile in choledochoscopy.

Persistent Cholangitis

The duration of postoperative pyrexia with body temperature over 37 C (mean ± SD) was 3.3 ± 2.7 days and the duration of postoperative hospital stay was 9.8 ± 5.1 days.

No patients had persistent fever and abnormal liver function tests after surgery to suggest persistent cholangitis.

Bile Cultures

Culture from common bile duct bile was positive in 64 patients (91.4%), with pure aerobes in 38 patients (54.2%), mixed aerobes in 20 patients (28.6%), mixed aerobes and anaerobes in five patients (7.1%), and pure anaerobes in one patient (1.4%). The most common aerobes isolated, either in pure or mixed growths, were *E. coli* in 43 patients (61.4%) *Klebsiella* sp. in 11 patients (15.7%), *S. faecalis* in six patients (8.6%), and *Proteus* sp. in five patients (7.1%). The most common anaerobes isolated were *Clostridium welchii* in four patients (5.7%) and *Bacteroides fragilis* in two patients (2.9%). Anaerobes were found only in patients who had previous biliary tract surgery or in patients with gangrenous cholecystitis.

Nine patients had previous cholecystectomy, and gall bladder bile was taken from 61 patients. Culture from gall bladder bile was positive in 54 patients (88.5%). The organisms isolated from the gall bladder bile were essentially the same as those isolated from the common bile duct bile.

Acute Pancreatitis

A preoperative serum amylase determination was diagnostic of acute pancreatitis in three patients. In two patients, the amylase level remained high after operation. No patients with a normal preoperative serum amylase level had clinical or biochemical evidence of acute pancreatitis develop as a result of choledochoscopy. Choledochoscopy had no adverse effects on the three patients with acute pancreatitis and stones in common bile ducts.

Choledochoscopic Views

Complete choledochoscopic examination was possible in all patients. A good, or at least a satisfactory, view could be obtained in all parts of the biliary tree in all patients. The surgeons considered the choledochoscopic views slightly affected by cholangitis because of the presence of inflammatory webs in five patients (7.1%).

Iatrogenic Injury to the Biliary Tree

There was no inadvertent injury to the biliary tree during choledochoscopy. In fact, the removal of impacted stones under direct vision caused less injury to the biliary tree.

Value of Choledochoscopy

Choledochoscopy detected overlooked common bile duct stones after conventional exploration of the common bile duct in 10 patients (14.3%) and it helped remove impacted stones that were not removed by traditional methods in two patients (2.9%).

Time Spent in Choledochoscopy

The time spent in choledochoscopy (mean ± SD) was 11.2 ± 3.5 minutes.

Incidence of Retained Common Bile Duct Stones after Choledochoscopy

Choledochoscopy failed to detect retained common bile duct stones only in one patient (1.4%) and this retained stone was detected on postoperative T-tube cholangiogram.

Wound and Intraperitoneal Sepsis

Five patients had deep wound infection develop within the first week after operation, whereas two patients had superficial wound infection develop on postoperative days 14 and 17, respectively. There was no intraperitoneal sepsis or abscess. Thus, the overall postoperative sepsis rate was 10%.

Culture from the infected wounds yielded pure aerobes in five patients and mixed aerobes in two patients. The most common organism isolated was *E. coli.*

Operative Mortality

There was no operative mortality in the 70 patients under study.

Discussion

Retained common bile duct stones represent a significant source of morbidity after choledocholithotomy. Although improved methods of retrieval and dissolution are now commonplace,[15] the cost and potential complications to the patient with retained common duct stones mandate the adoption of the most successful methods for complete removal of common duct stones at the initial operation. The conventional techniques of exploration of the common bile duct with the use of forceps, probes, or catheters have one common defect: they are blind procedures that rely on the surgeon's tactile sense alone and the surgeon is unable to see what he is doing. Some surgeons use postexploratory operative cholangiography but most have found it difficult to perform and to intepret and it is often omitted.[3] Moreover, because of its limitations, common bile duct stones can easily be overlooked.[23]

The choledochoscope offers many advantages during common bile duct exploration. By direct inspection, retained stones can be seen, "nonemptying" and "filling defects" on operative cholangiograms clarified, and latent pathologic lesions and anatomic abnormalities discovered. Furthermore, through the operative channel, biopsy of mucosal lesions and removal of impacted stones can be performed.[14,15] It is no wonder that good clinical results have been obtained with choledochoscopy. In the collected series of medical reports on choledochoscopy reviewed by Gartell and McGinn,[2] the incidence of retained common bile duct stones, with only a few exceptional reports,[5-7] was 0–3%.[2] There is no significant difference between the flexible and the rigid choledochoscopes in the reduction of retained stones,[2] despite that the view obtained with the rigid instrument is reported to be less extensive.[24,25]

Reports on intraoperative choledochoscopy focus on its value and safety mainly in elective operations.[1-14] Although the choledochoscopic appearances of the biliary tree in acute cholangitis were described,[4,26] indicating that it was used in acute cholangitis, there is still no solid data to suggest that this practice is safe and effective as there was no separate analysis of results of patients who had such a procedure.

Choledochoscopy in acute cholangitis theoretically increases the risks of operative and postoperative complications. Cholangiovenous reflux has been demonstrated in humans readily at common ductal pressures as low as 30 cm of water. Both bacteria and water-soluble substances pass readily from the bile ducts into the venous system above this pressure.[17] The amount of material refluxing was directly proportional to the pressure achieved in the bile duct,[16,17] resulting in bacteremia, endotoxemia, and septicemia if the refluxed bile was infected. Common duct pressure measurements during rigid choledochoscopy performed by us even at high cuff pressures showed that they never exceeded the safety limit of 25 cm of water recommended by Dellinger and his associates.[16] The performance of cholangiography by syringe injection resulted in common duct pressures that regularly exceeded 40 cm of water, and they frequently reached 80 cm of water transiently.[17] In this respect, choledochoscopy is safer than operative cholangiography and it can be used to replace it,[6,11] or to supplement it,[1,5] in the exploration of common bile ducts.

Our clinical results confirm that choledochoscopy is safe in acute cholangitis and acute suppurative cholangitis.[19,20] Choledochoscopy did not cause septicemia, worsen acute cholangitis, or provoke an attack of acute pancreatitis. There was no injury to the biliary tree by the choledochoscope and there was no operative mortality. The postoperative septic complication rate was acceptably low.[27] The effectiveness of choledochoscopy was not affected by cholangitis and the choledochoscopic views were good. The procedure was simple and the time spent was short. It was valuable in the detection of stones left after conventional methods of exploration of common bile duct, and such overlooked stones occurred in 10–27% of patients.[4,28] It also helped in the removal of impacted stones. Our incidence of retained common bile duct stones of 1.4% compared favorably with that of choledochoscopy in elective surgery.[1-14]

Although choledochoscopy is safe and effective in acute cholangitis and acute suppurative cholangitis,[19,20] it is still questionable whether it should be performed in patients with acute obstructive suppurative cholangitis, patients with serious associated medical diseases, or patients in poor general conditions. We believe that choledochoscopy is inadvisable in these patients with high surgical mortality as it prolongs the operation time and as a result increases the operative risks. The aim of surgery in these patients is to decompress the infected and obstructed biliary trees. Any retained common bile duct stones can subsequently be dealt with by methods of stone retrieval or dissolution[15] when the patients' conditions improve.

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Plasma Cholecystokinin and Pancreatic Polypeptide Response after Radical Pancreatoduodenectomy with Billroth I and Billroth II Type of Reconstruction

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This study was conducted to elucidate plasma cholecystokinin (CCK) and pancreatic polypeptide (PP) response after pancreatoduodenectomy and to compare response of CCK and PP in patients who had pancreatoduodenectomy with Billroth I and Billroth II type of reconstruction. Basal levels of plasma CCK were significantly lower in patients who had pancreatoduodenectomy (9.6 ± 0.8 pmol/L) than in the control (preoperative patients: 14.6 ± 2.0 pmol/L) probably because of the removal of the entire duodenum due to pancreatoduodenectomy, since vagotomy, which is concomitantly brought about by pancreatoduodenectomy, does not appear to interfere with release of CCK. Significant amounts of CCK (integrated CCK: 497 ± 111 pmol–120 min/L), although less amounts than in the preoperative patients (integrated CCK: 901 ± 167 pmol–120 min/L), were still released in response to oral fatty meal after pancreatoduodenectomy. Plasma CCK response to oral fatty meal was significantly greater in patients who had pancreatoduodenectomy with Billroth I type of reconstruction (integrated CCK: 705 ± 153 pmol–120 min/L) than in patients who had pancreatoduodenectomy with Billroth II type of reconstruction (248 ± 63 pmol–120 min/L). Simultaneous measurement of plasma levels of PP revealed complete abolishment of PP response by pancreatoduodenectomy. Since PP secretion can be produced by vagal stimulation, it is most likely that the decreased PP secretion is due to vagotomy rather than removal of the duodenum and pancreas. Significant amounts of CCK released after pancreatoduodenectomy, in which the main sources of release of CCK are removed, may suggest the compensatory mechanism of the remnant upper small intestine. This study also suggests the necessity of re-evaluating Billroth I type of anastomosis as a physiologic reconstruction procedure for the remnant alimentary tract after pancreatoduodenectomy.

ALTHOUGH SURVIVAL RATES after pancreatoduodenectomy for patients with cancer of the head of the pancreas still remain at low levels, the recent remarkable progress in the diagnostic screening tests, such as computed tomography, ultrasonography, and measurements of serum CA19-9 levels, have made it possible, to a certain extent, to detect a relatively early stage of pancreatic cancer,[1] resulting in the slight but gradual increase of the long-term survival rate after pancreatoduodenectomy. Cholecystokinin (CCK) is a well-known gastrointestinal hormone that plays a physiologic role not only in stimulating pancreatic enzyme secretion[2-4] and insulin release[5] but also in exerting a trophic effect on the pancreas.[6] It is, therefore, of great significance to investigate the plasma CCK response in patients with pancreatoduodenal resection to assess the exocrine and endocrine function of the remnant pancreas and to compare plasma CCK responses after different reconstructive procedures in pursuit of the most physiologically pertinent reconstruction of the alimentary tract after pancreatoduodenectomy.

Assumedly, CCK could exert an important role for the modulation of the function of the remnant pancreas even after pancreatoduodenal resection, but no information is available as to whether CCK is released into circulation after pancreatoduodenectomy, which removes the main sources[7] of release of CCK.

The current study was done to clarify changes in plasma CCK levels after pancreatoduodenectomy with special reference to the comparison of plasma CCK response after reconstruction of the alimentary tract with

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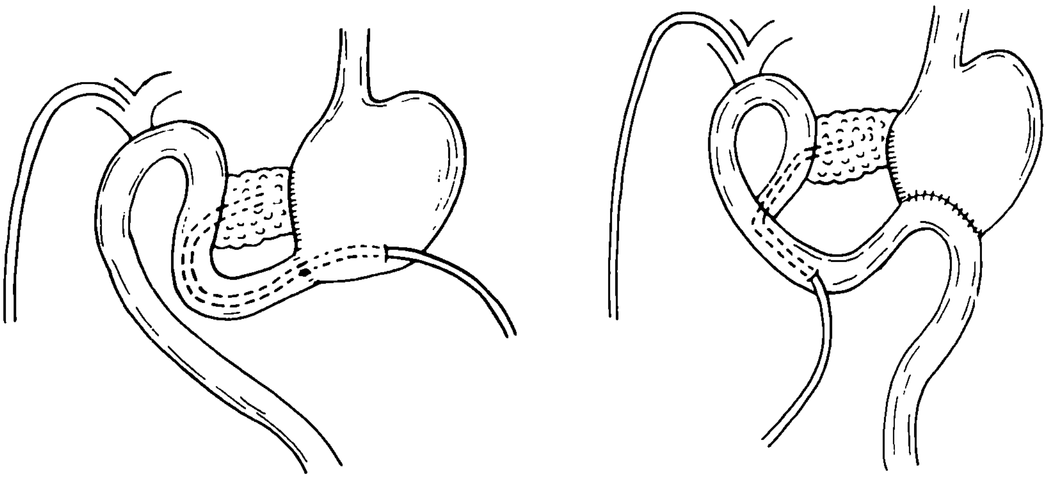

Billroth I type of Reconstruction

Billroth II type of Reconstruction

FIG. 1. Two types of reconstruction method for the alimentary tract after radical pancreatoduodenectomy in our department.

Billroth I and Billroth II type of anastomosis, both of which have been performed in our department (Fig. 1).

Simultaneous measurement of plasma levels of pancreatic polypeptide (PP), which plays a physiologic role for inhibition of exocrine pancreatic secretion,[8] was also done.

Materials and Methods

Eleven patients (8 men and 3 women) who had had pancreatoduodenectomy, ranging in age from 35 to 72 years with a median age of 56 years, were investigated. Included were seven patients with cancer of the head of the pancreas, two patients with cancer of the intrapancreatic common bile duct, one patient with cancer of papilla of Vater, and one patient with cancer of the duodenum, respectively. Radical pancreatoduodenectomy had been performed on these patients with *en bloc* resection of the head of the pancreas, entire duodenum, 5 cm of the upper jejunum, and distal half of the stomach, followed by cholecystectomy. The alimentary tract had been reconstructed either with Billroth I type of anastomosis (6 patients) or with Billroth II type of anastomosis (5 patients) (Fig. 1). Postoperative periods of these patients were 1 month (1 patient), 2 months (1 patient), 3 months (1 patient), and 12 months (3 patients) among patients with Billroth I type of reconstruction, and 1 month (1 patient), 2 months (1 patient), 3 months (1 patient), 6 years and 9 months (1 patient), and 6 years and 11 months (1 patient) among patients with Billroth II type of reconstruction, respectively. Postoperative courses in these 11 patients had been uneventful. Seven preoperative patients with early gastric cancer (2 men and 5 women), ranging in age from 51 to 71 years (mean: 62 years), were also studied as a control group for comparison with patients who had pancreatoduodenectomy. There was no pyloric stenosis in these preoperative patients.

After a 14-hour fast, patients who had pancreatoduodenectomy and preoperative patients were ingested with 200 mL of a fatty meal (chemically defined diet containing 14 g of fat; Clinimeal, Eisai Company, Japan). Peripheral blood samples were drawn before and serially at 10-minute intervals for 120 minutes after Clinimeal. Samples of blood were collected in tubes containing 50 KIU of Trasylol and 10 U of heparin per milliliter of blood and centrifuged at 3000 rpm with the constant temperature at 4 C for 15 minutes. The plasma was separated and stored at −20 C for future measurement of CCK and PP by specific radioimmunoassays.

Radioimmunoassay of CCK

Plasma levels of CCK was measured by means of a sensitive and specific radioimmunoassay for CCK-33 and CCK-39 that was developed by Thompson and Rayford,[3,9–12] using the CCK antibody (UT132), generously provided by Professor Phillip L. Rayford (Department of Physiology, University of Arkansas Medical Sciences, Little Rock, AR). The validation and details of

CCK radioimmunoassay conducted in our laboratory[13] are as follows.

CCK variant (CCK-39), supplied by Professor V. Mutt (Karolinska Institute, Sweden), was labeled (2.5 μg) with ^{125}iodine (1 mCi) by the chloramine-T method (25 μg/10 μL of chloramine T in 0.5 M potassium phosphate [PB] pH 6.0) for 60 seconds, followed by 62.5 μg/25 μL of sodium metabisulfite in 0.15 M PB. Labeled hormone was separated from other contaminants on an 11 × 0.9-cm Sephadex G-25 fine column (Pharmacia Fine Chemicals, Piscataway, NJ) eluted with 0.15 M PB containing 1 M NaCl (pH 6.0). ^{125}I-CCK-39 was further purified on a 4-cm column (Pasteur pipette) containing cellulose CF-11 (Whatman, Clifton, NJ) immediately before being used as a labeled tracer. Assay tubes were prepared with 200 μL of standards or plasma samples, 300 μL of phosphate buffer (0.02 M sodium phosphate, 0.15 M NaCl, 0.1% sodium azide, 0.5% normal rabbit serum, pH 6.8), 100 μL of antibody solution (final dilution 1:75,000), 100 μL of 0.1 M ethylenediaminetetraacetic acid (EDTA), and 100 μL of Trasylol (250 KIE/tube). The assay tube was then incubated for 24 hours at 4 C. Labeled CCK-39 (200 μL, 8000 cpm) was added to each tube and incubated for another 48 hours. The assay was terminated by an overnight incubation with goat antirabbit-γ globulin serum (Organon Teknika N.V., Malvern, PA).

The antibody bound 25–30%, 30–35%, and more than 75% of labeled CCK-39 at the final dilution of 75,000, 50,000, and 500, respectively, and nonspecific binding was less than 2%. Ten per cent inhibition of maximum binding (detection limit) was 1.6 ± 0.2 fmol/tube of standard CCK-33 and 50% inhibition (ID_{50}) was 13.4 ± 0.9 fmol/tube in five different assays. The intraassay variance was 8% and interassay variance was 10%. In this study, all samples were measured in duplicate in the same assay, and plasma CCK-33 levels were determined using standards containing 200 μL of hormone-free human plasma. When graded doses of CCK-33, CCK-39 (Professor V. Mutt), CCK-op (Dr. N. Yanaihara, Shizuoka, Japan), and synthetic human gastrin (G-17, Sigma, St. Louis, MO) were measured in the assay system, the slopes of the dose-response curve generated by CCK-33 and CCK-39 were −2.3 and −2.0, respectively. Estimation of ID_{50} revealed that CCK-33 and CCK-39 were almost equally potent. In contrast, the slopes of the dose-response curve for G-17 and CCK-op were −0.58 and −0.46, respectively, and the potency of both peptides was less than 0.5% when compared with that of CCK-33 at ID_{50}. No cross-reactivity was observed with structurally unrelated gastrointestinal peptides such as secretin, GIP, VIP, substance p, PYY, neuromedin C, or GRP. Serial dilutions of dog postprandial plasma (25–200 μL) and duodenal extracts (1:200–1:3200) produced parallel dose-response curve compared with that of standard CCK-33.

The comparison of dose-response curves generated by CCK standard diluted with or without 200 μL of hormone-free plasma clarified that the slopes and ID_{50} of CCK standard diluted with hormone-free dog plasma, with hormone-free human plasma, and with buffer (without hormone-free plasma) are −2.0 and 11.1 fmol/tube, −1.8 and 15.1 fmol/tube, and −1.8 and 9.9 fmol/tube, respectively, demonstrating that this assay system is free from the influence of interference substances in the plasma.

Radioimmunoassay of PP

Plasma PP levels were measured by specific radioimmunoassay[14] using rabbit anti-h PP serum, kindly donated by Dr. R. E. Chance (Lilly Research Laboratories, Eli Lilly Co., Indianapolis, IN).

The results of this study are expressed as mean ± SEM. Student's paired or unpaired t-test was used to analyze the data for statistical differences. Differences with a p value of less than 0.05 were considered significant.

Results

Basal Plasma Levels of CCK

Mean basal plasma levels of CCK in the pancreatoduodenectomy group (11 patients) (9.6 ± 0.8 pmol/L) were significantly lower than those observed in the control group (7 preoperative patients) (14.6 ± 2.0 pmol/L). No significant difference was noted between mean basal plasma CCK levels in the pancreatoduodenectomy group reconstructed with Billroth I type of anastomosis (6 patients) (8.9 ± 0.6 pmol/L) and Billroth II type of anastomosis (5 patients) (10.4 ± 1.0 pmol/L).

Plasma CCK Response

In the control group (preoperative patients), in response to oral fatty meal, incremental values of CCK (ΔCCK) were significantly increased to 3.7 ± 1.3 pmol/L at 5 minutes, attained the peak of 11.7 ± 3.3 pmol/L at 20 minutes, and then remained significantly elevated up to 120 minutes. In the pancreatoduodenectomy group, ΔCCK values were also significantly elevated after oral fatty meal, showing the peak value of 7.2 ± 1.5 pmol/L at 20 minutes. Although ΔCCK values remained significantly elevated throughout the study, plasma CCK response in the pancreatoduodenectomy group was lower than that observed in the preoperative group (Fig. 2). The integrated CCK in the pancreatoduodenectomy group (497 ± 111 pmol-120 min/L) was significantly less than that noted in the control group (901 ± 167 pmol-120 min/L) (Fig. 3).

Plasma CCK response to oral fatty meal was com-

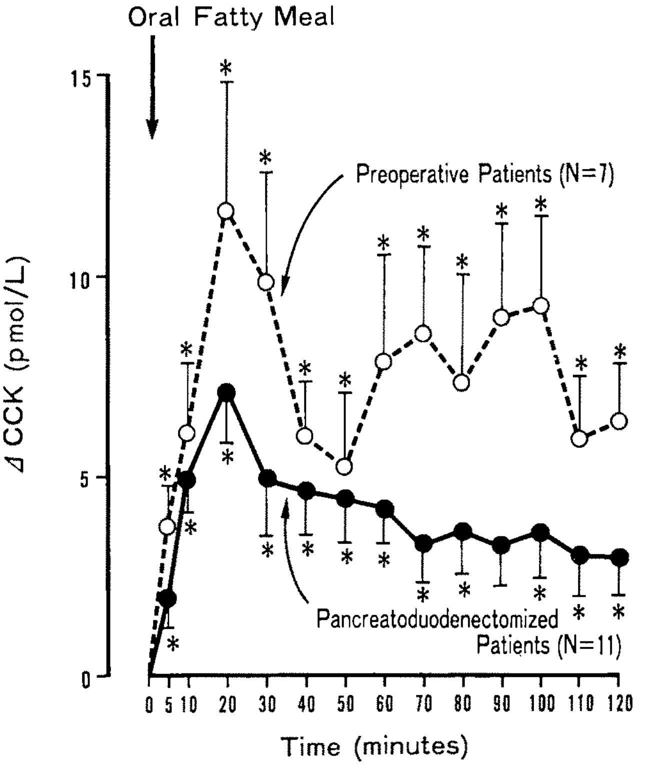

FIG. 2. Comparison of the plasma CCK response to oral fatty meal in preoperative patients and patients who had pancreatoduodenectomy. Asterisks indicate significant elevation above basal.

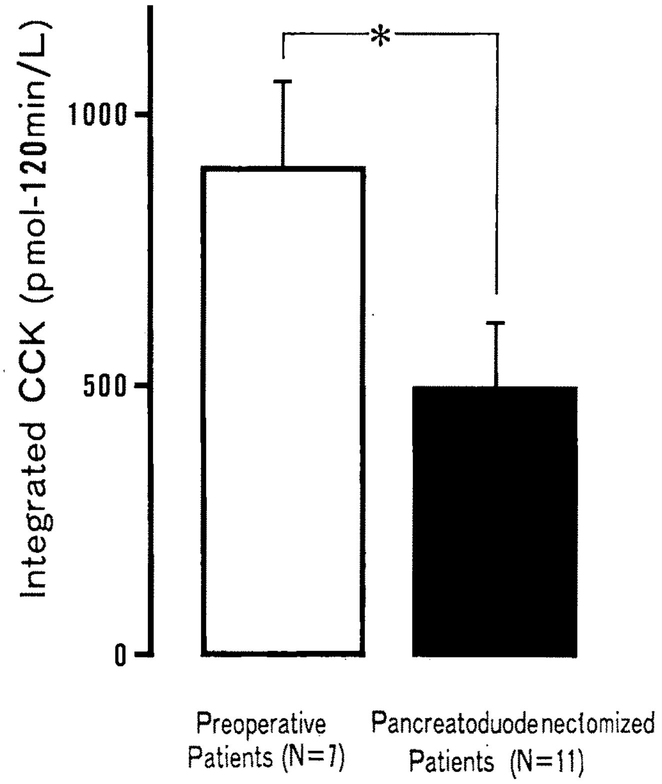

FIG. 3. Integrated CCK in preoperative patients and patients who had pancreatoduodenectomy. Asterisk indicates significant difference in integrated CCK between preoperative patients and patients who had pancreatoduodenectomy.

pared among patients who had pancreatoduodenectomy with Billroth I and Billroth II type of anastomosis (Fig. 4). Patients with Billroth I type of anastomosis showed a rapid and greater plasma CCK response when compared with plasma CCK response in patients with Billroth II type of anastomosis. In patients with Billroth I type of reconstruction, ΔCCK values rose significantly to the maximum of 10.8 ± 1.7 pmol/L at 20 minutes and then gradually began to fall, however, remaining elevated up to 100 minutes. On the other hand, patients with Billroth II type of reconstruction showed a delayed and lower plasma CCK response compared with that noted in patients with Billroth I type of reconstruction; significant increase in ΔCCK values was achieved at 30, 40, 50, 60, 110, and 120 minutes after oral fatty meal (Fig. 4). The integrated CCK was significantly greater in patients who had pancreatoduodenectomy with Billroth I type of reconstruction (705 ± 153 pmol–120 min/L) than in patients who had pancreatoduodenectomy with Billroth II type of reconstruction (248 ± 63 pmol–120 min/L) (Fig. 5).

Basal Plasma Levels of PP

The mean basal plasma level of PP in the control group was 35 ± 8 pmol/L. In contrast, basal plasma levels of PP were undetectable (below detection limit) in

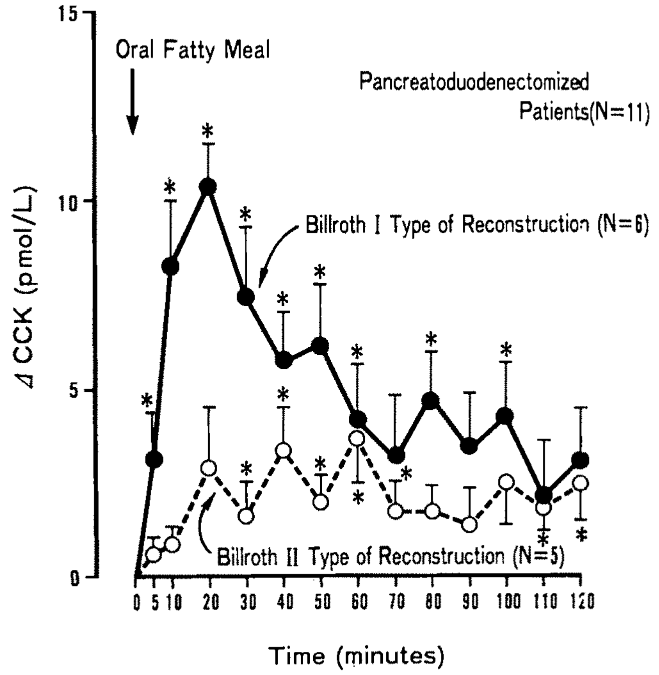

FIG. 4. Comparison of the plasma CCK response to oral fatty meal in patients who had pancreatoduodenectomy with Billroth I and Billroth II type of reconstruction. Asterisks indicate significant elevation above basal.

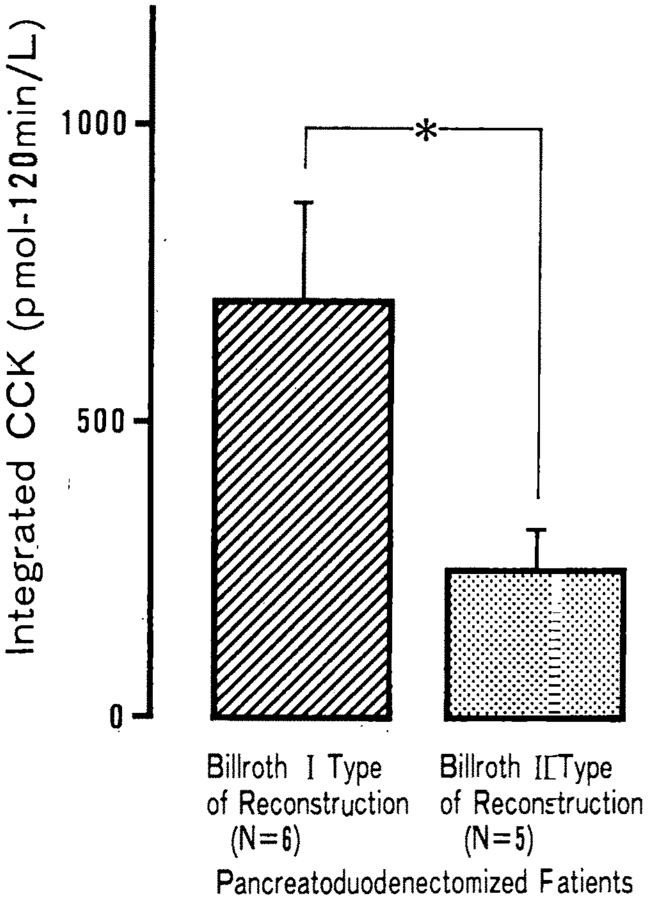

FIG. 5. Integrated CCK in patients who had pancreatoduodenectomy with Billroth I and Billroth II type of reconstruction. Asterisk indicates significant difference in integrated CCK between Billroth I and Billroth II type of reconstruction.

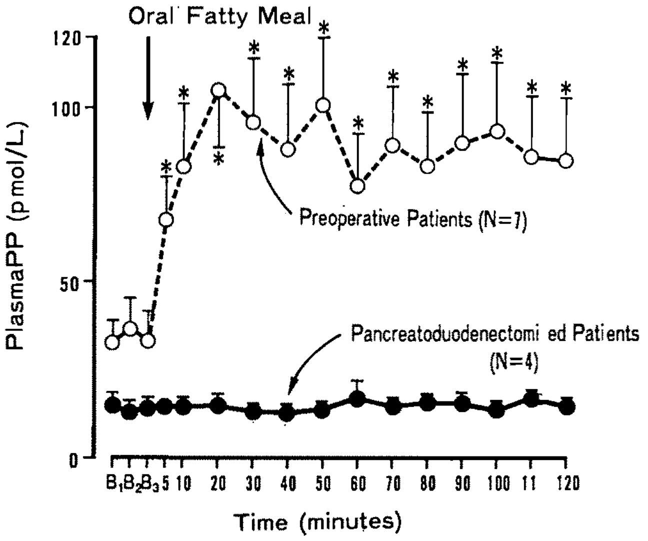

FIG. 6. Comparison of the plasma PP response to oral fatty meal in preoperative patients and patients who had pancreatoduodenectomy. Asterisks indicate significant elevation above basal.

seven of 11 patients with pancreatoduodenal resection. The mean basal plasma level of PP in four patients in whom PP levels were detectable (16 ± 1 pmol/L) was significantly less than that found in the control group (Fig. 6).

Plasma PP Response

Plasma PP in preoperative patients showed a rapid and significant increase in response to oral fatty meal; significant elevation was achieved at 5 minutes (68 ± 14 pmol/L) and remained significantly elevated up to 120 minutes. On the contrary, patients with pancreatoduodenal resection did not show any increase in plasma PP levels after ingestion of a fatty meal (Fig. 6).

Discussion

The role of hormonal factors, especially that of CCK, is supposedly of great importance in modulating the exocrine and endocrine function[2–6] of the remnant pancreas after pancreatoduodenal resection that is performed on patients with periampullary cancer, since radical pancreatoduodenectomy is inevitably accompanied by vagotomy. The effect of vagotomy on gastrointestinal hormones has been widely documented.[15–21] To evaluate whether CCK release is under vagal control, Guzman and colleagues[17] electrically stimulated the vagus nerves of anesthetized dogs and found increased pancreatic protein secretion, but no increase in plasma levels of CCK, indicating that CCK release is not under vagal control and that vagal stimulation of pancreatic secretion occurs through a mechanism independent of CCK. They have also demonstrated that vagotomy has no effect on the release of CCK.[18] This observation is inconsistent with reports by Fried and colleagues who have shown that CCK secretion in response to intraduodenal oleate[19,20] or to exogenous bombesin[20] or CCK[20] was not significantly affected by vagotomy. On the other hand, PP secretion is predominantly mediated through the vagal cholinergic pathways. Modlin and colleagues[21] have demonstrated that the release of PP is inhibited to a significantly greater extent by vagotomy than by atropine. Prominent decrease of PP secretion by vagotomy has been also confirmed by Guzman and colleagues[18] and by Fried and colleagues.[20] However, to our knowledge, radioimmunoassay measurement of plasma levels of CCK and PP after pancreatoduodenectomy has not been performed. The current study revealed that basal concentrations of plasma CCK were significantly lower in patients who had pancreatoduodenectomy than in the preoperative patients. This relatively low basal level of plasma CCK after pancreatoduodenal resection could be possibly attributed to the elimination of the entire duodenum in which CCK producing cells are most numerously distributed,[7] since vagotomy does not appear to interfere with release of CCK. Despite the low fasting secretion of CCK in patients who had pancreatoduodenectomy, this study demonstrates that significant amounts of CCK, although less amounts than in the preoperative patients, are still released postprandially even after pancreatoduodenectomy, which removes the main sources of release of CCK, suggesting that this phenomenon may reflect the compensatory mechanism of the remnant upper small intestine. Plasma responses of other hormonal factors, such as secretin, gastrin, and gastric inhibitory polypeptide, in patients who had pancreatoduodenectomy have also been documented; diminished secretin response to the ingestion of hydrochloride solution,[22] food,[23] no response of gastrin to intravenous infusion of arginine,[22] and almost the same response of gastric inhibitory polypeptide to oral glucose as observed in the control group.[24] In these reports, however, reconstruction of the alimentary tract after pancreatoduodenectomy has been performed with Billroth II type of anastomosis (modified Child method).

There have been two types of reconstruction procedure for the remnant alimentary tract after pancreatoduodenectomy; Billroth I type (Cattell[25] and Imanaga[26]) and Billroth II type (Whipple[27] and Child[28]).

In our department, we have been performing Billroth I type of anastomosis as well as Billroth II type of anastomosis after pancreatoduodenal resection as represented on Figure 1. One of the original aspects of Billroth I type of reconstruction procedure in our department lies in the retrocolic approach for the anastomosis of the remnant alimentary tract after pancreatoduodenectomy. The unique Billroth I type of reconstruction procedure after pancreatoduodenectomy was started about 7 years ago in our department, since it was conceivable that the passage of food through the entire remnant upper small intestine was more physiologic than food bypassing the upper portion of the remnant small intestine in view of the release of gastrointestinal hormones, which presumably play a significant role in the modulation of the function of the remnant alimentary tract.

The current study first did a comparative study on the plasma response of gastrointestinal hormones in patients who had pancreatoduodenectomy with Billroth I type and II type of anastomosis. The interesting phenomenon that plasma CCK response was significantly greater in patients who had pancreatoduodenectomy with Billroth I type of anastomosis than in patients with Billroth II type of anastomosis may support the hypothesis that after pancreatoduodenectomy, Billroth I type of reconstruction method is a more physiologic procedure than Billroth II type of reconstruction because CCK could exert a trophic effect[6] on the remnant pancreas as well as play an important role in the regulation of exocrine[2-4] and endocrine[5] function. Approximately 100 pancreatoduodenal resections have been performed in our department over the last 7 years from 1979 to 1985. Comparative studies on surgical complications after pancreatoduodenectomy in our department revealed that there was no significant difference between Billroth I and Billroth II type of reconstruction in both morbidity and mortality after pancreatoduodenectomy, except that intermittent fever due to the late stage of biliary infection was more frequently observed after Billroth II type of reconstruction.

It has been controversial relating to the molecular forms of CCK in the circulation and physiologic importance of CCK-33 and CCK-8. Recent studies by Solomon et al.[29] and Konturek et al.[4] have clarified that larger molecular forms of CCK is quantitatively the most important mediators of CCK action on the pancreas. The antibody used in this study has its greatest affinity for larger forms of CCK (CCK-33 and CCK-39) and has little or no affinity for the smaller forms of this peptide.[3,9-13] The same CCK antibody that was used in the current study has been proved to inhibit not only the stimulatory effects of pure CCK and extracts of the duodenum on gallbladder contraction[11] but also the bioactivity of both exogenously administered and endogenously released CCK on the pancreas,[3] supporting the concept that larger forms of CCK are mediators of the two major biologic actions of CCK.

In contrast to plasma CCK response, pancreatoduodenectomy completely abolished plasma PP response. Basal plasma levels of PP were even undetectable in seven of 11 patients who had pancreatoduodenectomy. Since PP secretion is to a great extent mediated through the vagal cholinergic pathways,[18,20,21] it is most likely that the decreased PP secretion is due to vagotomy rather than removal of the duodenum and pancreas. PP originates from cells localized almost exclusively in the pancreas.[30] Regional differences in PP distribution exist, with PP found predominantly in the uncinate process and head of the pancreas.[31] Total pancreatectomy has been reported to abolish the increase in circulating PP seen after a meal, which led to the suggestion that the pancreas is the only site of PP release.[32] The complete abolishment of PP release even after pancreatoduodenectomy, which preserves most of the left lobe (body and tail) of the pancreas, might be partly attributed to the predominant distribution of PP cells in the right lobe of the pancreas.

In conclusion, this study demonstrates that significant amounts of CCK, but not PP, are released even after pancreatoduodenectomy, which removes the main sources of release of CCK, suggesting the compensatory mechanism of the remnant upper small intestine. Significantly greater CCK response in patients who had pancreatoduodenectomy with Billroth I type of reconstruction than in patients with Billroth II type of reconstruction might prompt us to re-evaluate Billroth I type of anastomosis as a more physiologic reconstruction procedure for the alimentary tract after pancreatoduodenectomy.

Acknowledgments

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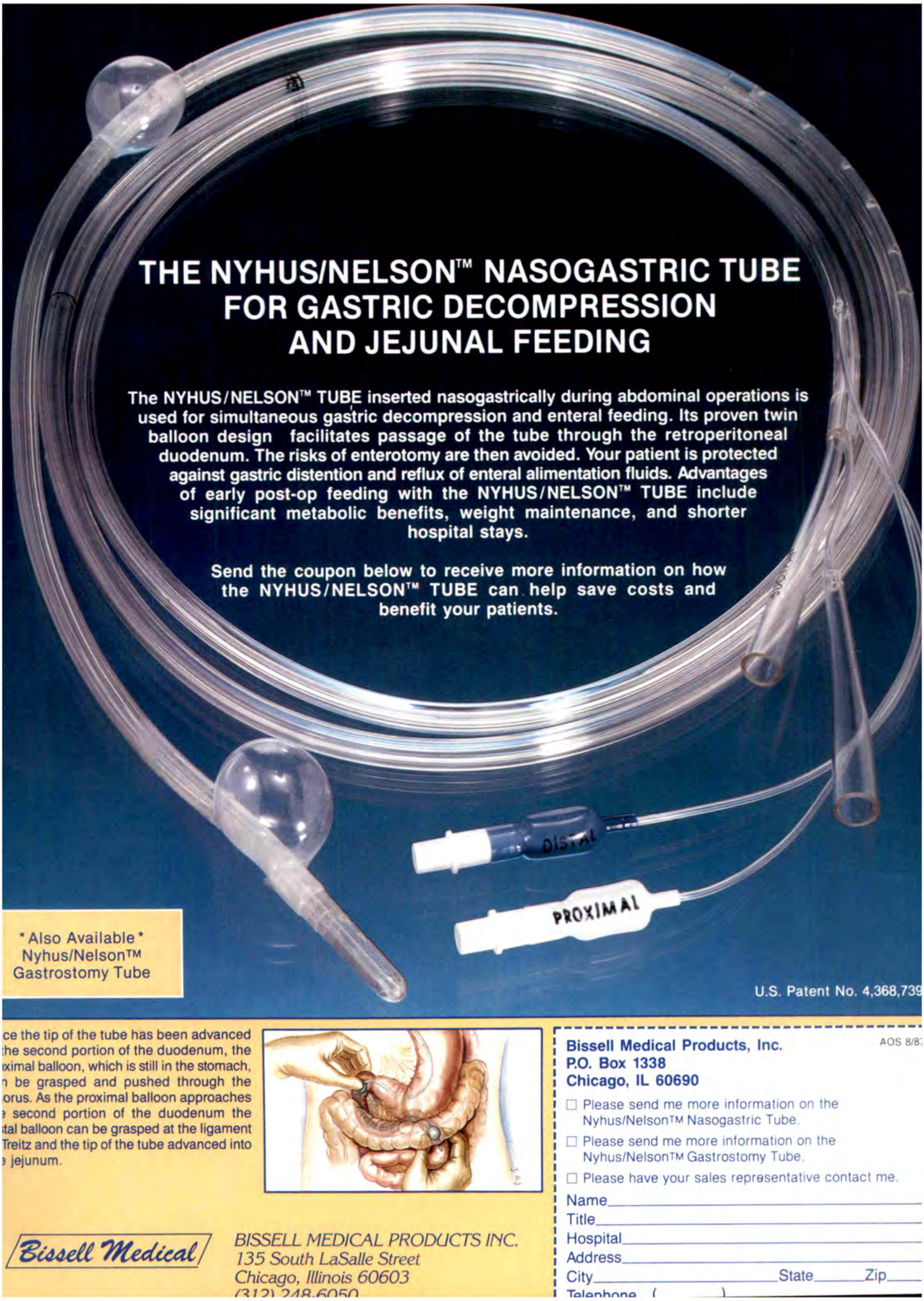

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CASE # 24 **AGE:** 55 **SEX:** FEMALE

DIAGNOSIS: CECAL CARCINOMA

SYMPTOMS: ANEMIA (Hg 6 gm/dl)

OPERATION: RIGHT HEMICOLECTOMY & GASTROSTOMY

The patient had a right hemicolectomy with stapled (U.S. Surgical Corp) anastomosis and fascia closure and a MOSS® gastrostomy tube. The stomach and proximal duodenum were aspirated, with immediate simultaneous feeding into the distal duodenum.

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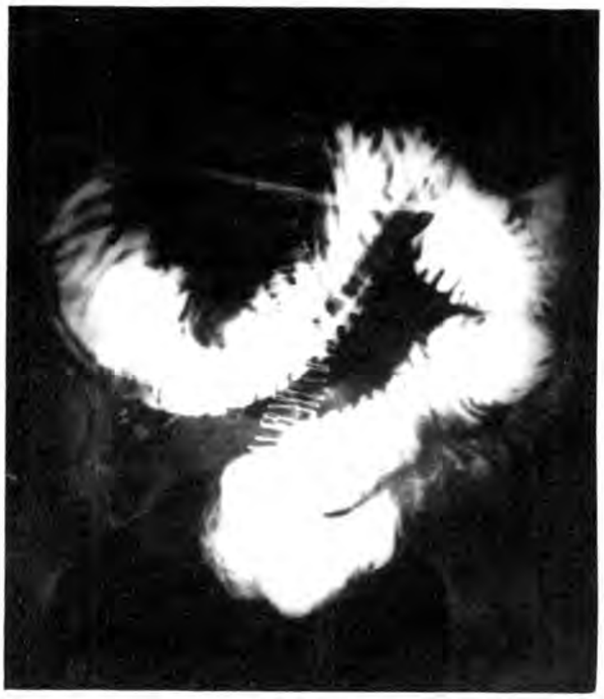
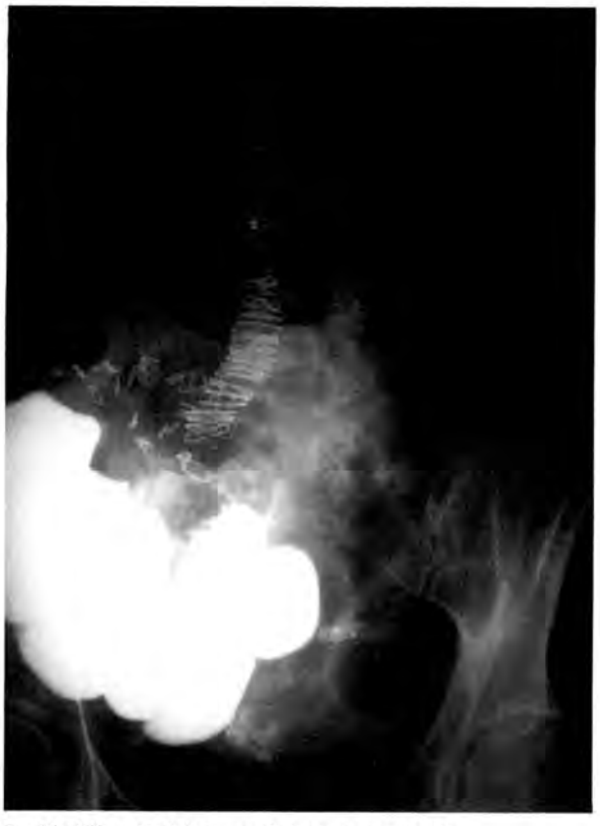
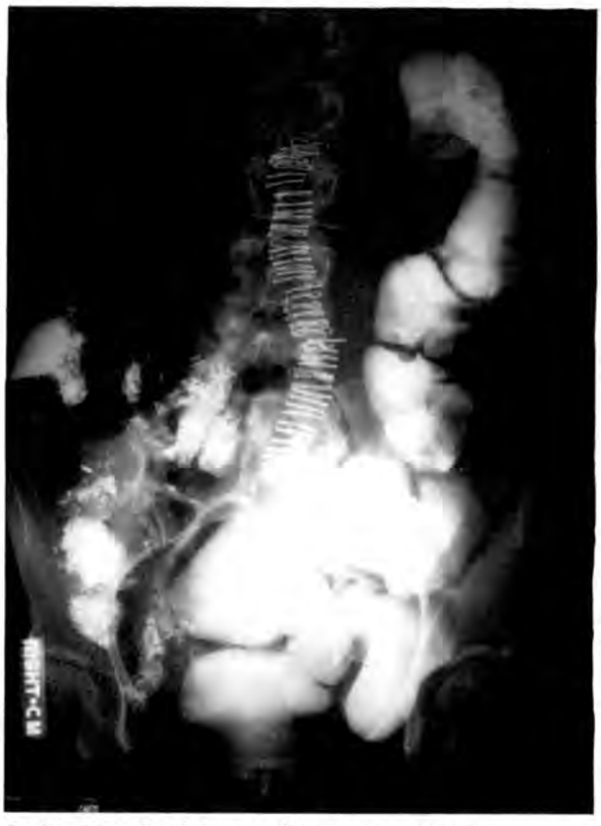
She received 300 ml/hr of Vivonex TEN (Norwich Eaton Pharm), absorbed 5,000 kcal the initial 20 hours, and then tolerated a general diet. She was the 4th patient discharged uneventfully 24 hours after bowel resection and reanastomosis.



A. Study @ 5 minutes (5 hours postop).
Note efficient removal of all excess barium, with none reaching the stomach.



B. Motility @ 4 hours (9 hours postop).
All barium is within the ileum.



C. Motility @ 16 hours (21 hours postop).
Barium is exiting in a spontaneous bowel movement.

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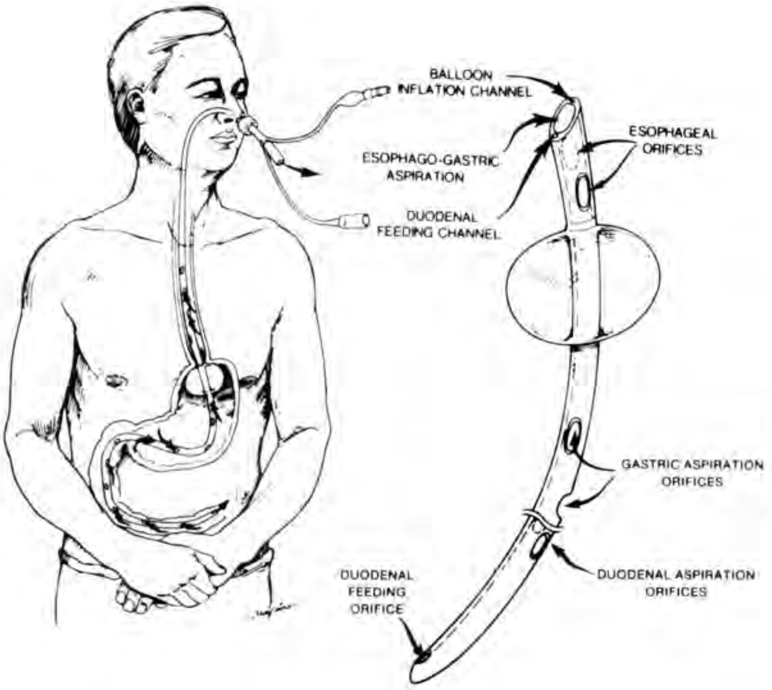
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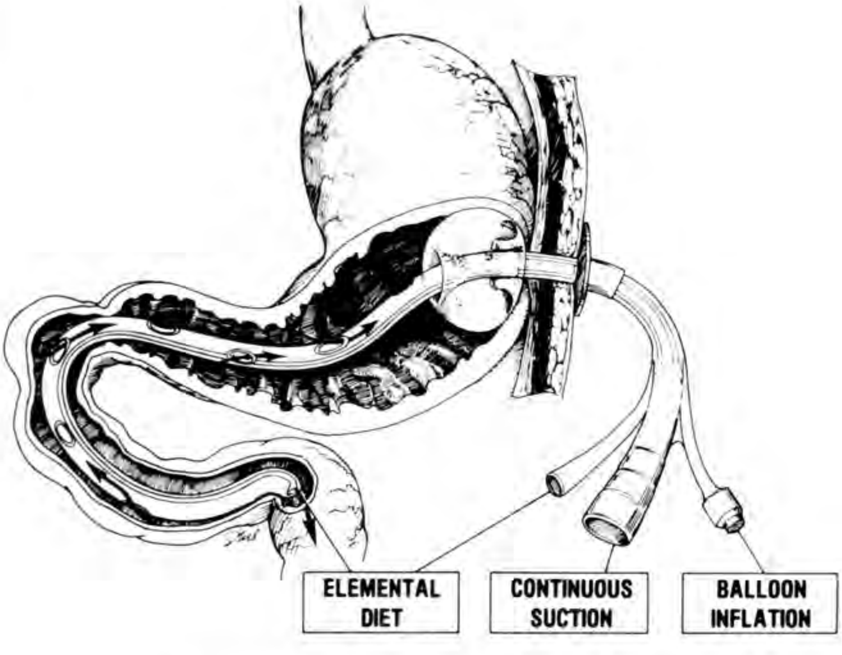

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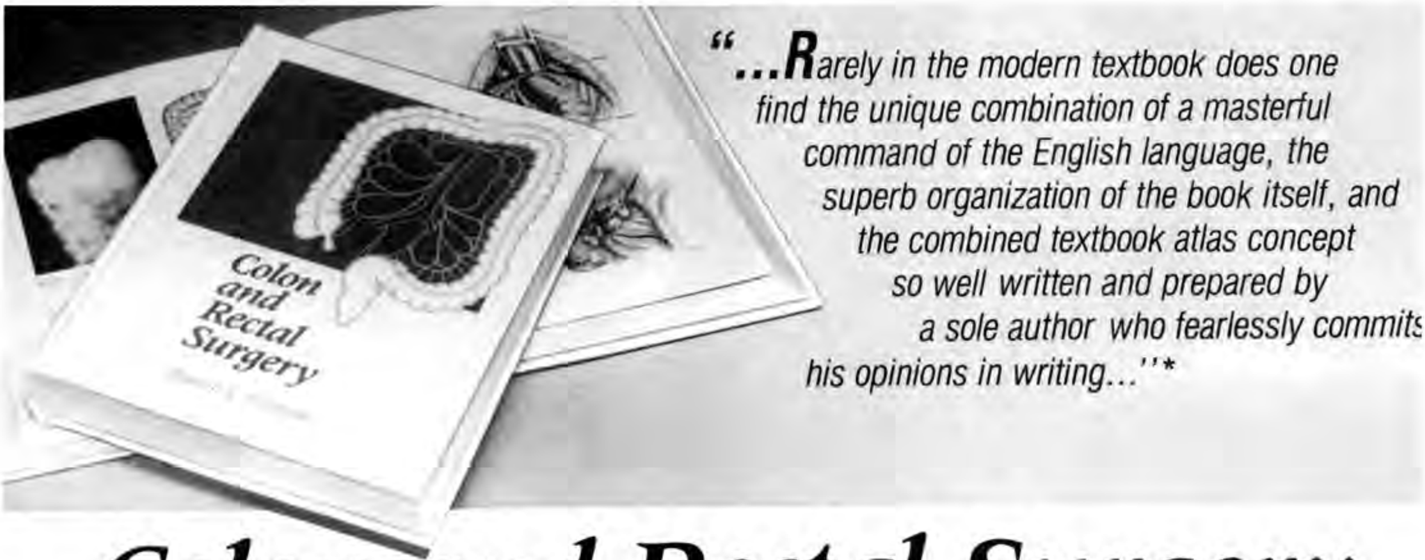

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The Comparative Influence of Prophylactic Antibiotics on the Prothrombin Response to Warfarin in the Postoperative Prosthetic Cardiac Valve Patient

Cefamandole, Cefazolin, Vancomycin

DAVID M. ANGARAN, M.S., VIRGIL C. DIAS, PHARM.D., KIT V. AROM, M.D., WILLIAM F. NORTHRUP, M.D., THOMAS G. KERSTEN, M.D., WILLIAM G. LINDSAY, M.D., and DEMETRE M. NICOLOFF, M.D.

From the United Hospital Heart Institute, United Hospital, St. Paul, Minnesota

A prospective randomized trial was conducted comparing the effect of three antibiotics: cefamandole (CM), cefazolin (CZ), and vancomycin (V), used as prophylaxis for prosthetic valve surgery, on the prothrombin (PT) response to warfarin (W) on the third day of anticoagulant therapy. Twenty patients, with normal preoperative PTs, were randomized to each antibiotic. Their PTs were not significantly different at 2 hours after operation and the morning before W was begun. The three groups received similar W doses for 2 days, and the PT, as percentage of activity, on the morning of the third day demonstrated that V (51 ± 18%) was significantly greater ($p < 0.005$) than CM (29 ± 14%) or CZ (38 ± 18%). CM had a significantly greater percentage of change in PT (64 ± 14%, $p < 0.0001$) from the first to third day than either CZ (51.1 ± 18%) or V (44.6 ± 19%). CM also had a greater number of patients (6) with PTs ≥ 30 seconds on day 3 than either CZ (1) or V (1). The antibiotic influence on the PT response to W in this study is ranked as CM > CZ > V.

THE FIRST-GENERATION cephalosporins (*e.g.*, cephalothin, cefazolin) have been widely used as the antibiotic of choice for prophylaxis of surgical infections. These antibiotics have been reported to cause hypoprothrombinemia in patients receiving long-term antibiotic therapy with a poor dietary intake or in renal failure.[1-3] More recently, the second-generation cephalosporins, such as cefamandole, have enjoyed wide popularity in prophylaxis of heart surgery because of their extended gram-negative spectrum and activity against *Staphylococcus aureus* and *Staphylococcus epidermidis*. Cefamandole contains the 1-N-methyl-5-thiotetrazole (MTT) group that has been implicated as a cause of accelerated prothrombin (PT) depletion associated with episodes of both major and minor bleeding.[4,5] Vancomycin, a noncephalosporin antibiotic with only a gram-positive spectrum, has not been implicated as a cause of hypoprothrombinemia.[6]

For patients who have prosthetic valve replacement surgery, adequate anticoagulation is of vital importance in prevention of thromboembolic complications. The type of prophylactic antibiotic administered to these patients during and after surgery could influence the response to subsequent warfarin anticoagulation therapy.

We have reported a retrospective investigation comparing the PT response to warfarin in patients undergoing prosthetic valve surgery who received either cefamandole or vancomycin. This study indicated that patients receiving cefamandole had a significantly greater hypoprothrombinemic response after the first 2 days of warfarin therapy when compared with patients administered vancomycin.[7]

To confirm this retrospective work, we conducted the following prospective randomized, open-label trial comparing the effect of cefamandole, cefazolin, and vancomycin as prophylactic antibiotics on the PT response to warfarin in patients who had prosthetic valve surgery.

Methods

Sixty patients who were scheduled to have cardiac valve replacement surgery were prospectively assessed and randomly assigned by a random number table to receive either cefamandole, cefazolin, or vancomycin for surgical prophylaxis. All patients with a history of either a penicillin or cephalosporin allergy were assigned to receive vancomycin. The study was approved by the

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Supported by a grant from Eli Lilly and Company and warfarin plasma levels by E. I. duPont de Nemours and Company.

Reprint requests: David M. Angaran, M.S., R.Ph., Director, Biomedical Research, United Hospital Heart Institute, 333 North Smith Avenue, St. Paul, MN 55102.

Submitted for publication: February 3, 1987.

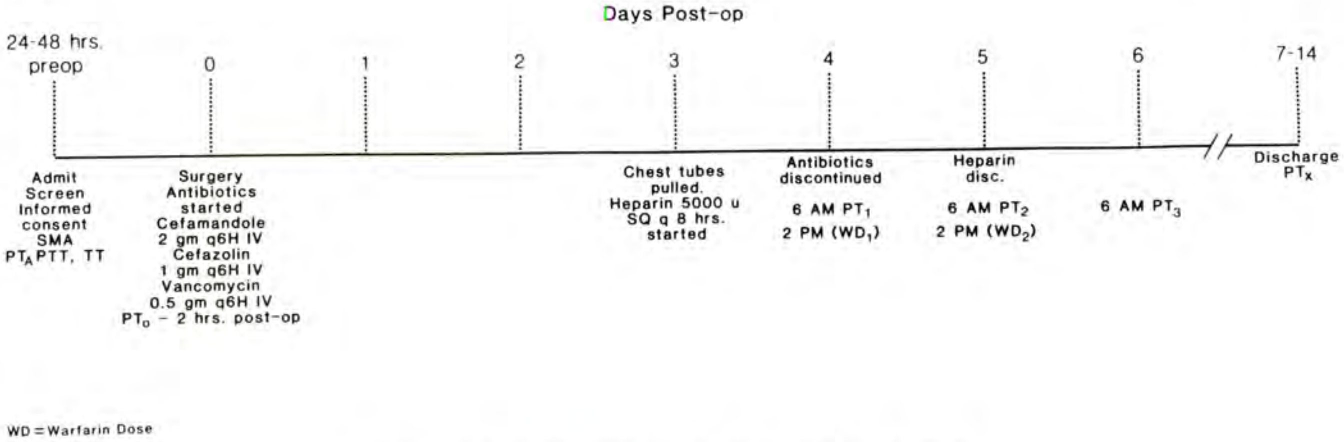

FIG. 1. The typical hospital course for a prosthetic valve patient.

Institutional Review Board and informed consent was obtained the day before surgery.

Preoperative exclusion criteria were: (1) PT 2 seconds greater than control, platelets $< 150{,}000$ cells/μL, PTT greater than normal, thromboplastin time (TT) 2 seconds greater than control; (2) a history of active liver disease; (3) a serum creatinine level of >2 mg/dL, BUN > 40 mg/dL; and (4) emergent surgery due to rapidly worsening heart failure or bacterial endocarditis.

Patients were excluded in the postoperative period if they: (1) had a serum creatinine level of >2 mg/dL, BUN > 40 mg/dL; (2) experienced prolonged cardiovascular instability requiring vasopressors, vasodilators, intravenous inotropes, and/or intra-aortic balloon pump for more than 48 hours after operation; and (3) had liver impairment or hepatitis.

One team of five cardiovascular surgeons following a uniform protocol performed all surgeries in a single hospital. Surgical data were obtained from the anesthesia record, cardiopulmonary bypass record, and the operative reports. All patients received identical anesthetic agents, including pancuronium, fentanyl, ketamine, enflurane, and diazepam. A St. Jude's medical cardiac valve prosthesis was used in all patients. Cardiac pulmonary bypass was accomplished using moderate systemic hypothermia (28 C) and cold potassium cardioplegia. Cefamandole, 2 g, cefazolin, 1 g, or vancomycin, 0.5 g, were administered intravenously as the prophylactic antibiotic before the chest incision and every 6 hours up to 24 hours after chest tube removal.

The typical hospital course of these patients including surgery and postoperative recovery is outlined in Figure 1. Warfarin was the only oral anticoagulant used and administered at 2:00 P.M. each day. The PT was measured: on admission 24–48 hours before operation (PT_A); after operation immediately on return to the intensive care unit (PT_O); at 6:00 A.M. the beginning day of warfarin therapy (PT_1); and daily throughout the hospital stay. Warfarin therapy and dosage selection was at the discretion of the attending cardiologist and adjusted with a PT goal of 1.5–2 times control. The initial warfarin dose was 10 mg in 67% of patients. A PT was also obtained daily for 2 or 3 consecutive days (PT_B) between PT_O and PT_1 in nine patients who received cefamandole, in nine patients who received cefazolin, and in 12 patients who received vancomycin. The PT per cent change (PT%C) was computed by $PT_1\%A - PT_3\%A / PT_1\%A \times 100$.

The PT was measured by the Quick method using a Dade Thromboplastin-C reagent and processed using an MLA Electra-700 automatic coagulation timer (American Scientific Products, McGaw Park, IL) with a coefficient of variation (CV) of 1.8% at normal control and 4% CV at high control. The percentage of prothrombin activity (PT%A) was obtained by converting the PT in seconds to percentage activity by means of a calibration curve obtained from the laboratory. This relationship between PT seconds and PT%A is nonlinear as seen in Figure 2.

Warfarin plasma concentrations were determined by a reverse-phase, high-performance liquid chromatography (HPLC). Warfarin and the internal standard, p-chloro-warfarin, were extracted from acidified, citrated plasma with cyclopentane. The organic layer was evaporated and the residue was reconstituted with 200 μL of mobile phase consisting of 57% acetonitrile/43% water, pH 3.0. An aliquot was injected onto a DuPont Zorbax® C column (E. I. duPont de Nemours and Co., Inc., Wilmington, DE) and the effluent was monitored at 280 nm with a Waters® 440 absorbance detector (Millipore, Waters Chromatography Division, Milford, MA). Concentrations were directly proportional to the absorbance, and as little as 0.1 μg/mL warfarin could be detected in 200 μL of plasma. The assay was linear from

0.1 to 10.0 μg/mL with an absolute recovery greater than 80%. Intra-day assay CV ranged from 2.2 to 11.1% over a concentration range from 0.1 to 10.0 μg/mL. Standards assayed over a 6-month period had CVs ranging from 0.5 to 14.5%.[8]

Patients were assigned to a New York Heart Association (NYHA) functional class using the standard published criteria.[9]

The ANOVA with the Neuman–Keuls multiple range test was used to compare the means of the three groups, and linear regression was used for statistical evaluation of the data. Unless otherwise stated, all data are reported as the mean ± SD. Statistical significance was designated at the $p \leq 0.05$ level.

Results

The demographic data describing the three groups as listed in Table 1 indicate the groups were well matched for sex and type of surgery. The patients who received cefamandole and cefazolin were significantly older than those receiving vancomycin. The NYHA classification of cardiovascular status was similar for the three groups, with the majority (70%) in Class III. Some of the more important parameters that were assessed and not found to be significantly different among the three groups are: (1) sex, (2) PT$_A$, (3) PT$_O$, (4) time on cardiopulmonary bypass, (5) length of surgery, (6) time of anesthesia, (7) total blood loss during and 24 hours after surgery, and (8) serum albumin level.

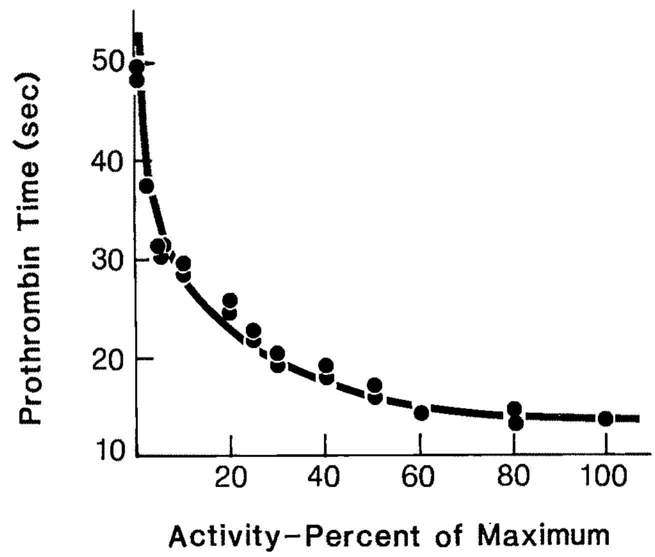

FIG. 2. Prothrombin percent activity: second relationship. The relationship between per cent activity and the prothrombin time in seconds is curve linear on a linear–linear scale.

Five patients received potentially interacting drugs in the postoperative period. They were cefamandole (2 patients: 1 quinidine, 1 cimetidine), cefazolin (1 patient: cimetidine), and vancomycin (2 patients: 1 quinidine and 1 cimetidine). Quinidine and cimetidine may potentiate the effects of warfarin.[10] Removing these patients from their respective groups did not alter any of the statistical values; therefore, they are included in all the reported results.

TABLE 1. *Demographic Data for 60 Prosthetic Valve Patients*

	Cefamandole N = 20	Cefazolin N = 20	Vancomycin N = 20
Sex M/F	10/10	14/6	12/8
Age (years)	64.3 ± 13§	62 ± 9.5§	56 ± 10.5
Type of surgery			
CAB with AVR	2	5	4
CAB with MVR	3	2	3
AVR	11	7	9
MVR	3	5	4
AVR with MVR	1	0	0
CAB with AVR and MVR	0	1	0
NYHA class			
I	0	1	1
II	3	5	2
III	15	12	15
IV	2	2	2
PT$_A$* (%A)†	88.4 ± 9.3	88.3 ± 11.3	90.3 ± 8.5
PT$_O$‡ (%A)	52 ± 4.0	54 ± 3.6	51 ± 4.1
Time of bypass (min)	105 ± 46	107.3 ± 41	113 ± 70
Length of surgery (min)	203 ± 112	210.7 ± 56	210.9 ± 108
Anesthesia time (min)	308 ± 159	283 ± 65	384.8 ± 130
Blood loss during surgery (ML)	1038 ± 814	1022 ± 680	1069 ± 1152
Preoperative albumin (g/dL)	3.8 ± 0.3	3.8 ± 0.4	4.2 ± 0.4

* PT$_A$ = admission 24–48 hours before operation.
† (%A) = percent prothrombin activity.
‡ PT$_O$ = 2 hours after operation.
§ Cefamandole, cefazolin > vancomycin, $p < 0.05$.

CAB = coronary artery bypass.
AVR = aortic valve replacement.
MVR = mitral valve replacement.

TABLE 2. *The Prothrombin Percent Activity (PT%A), Warfarin Doses, and Serum Levels for the 60 Prosthetic Valve Surgery Patients*

	Cefamandole N = 20	Cefazolin N = 20	Vancomycin N = 20
PT_1 (%A)*	80 ± 18	82 ± 12	90 ± 12
PT_3 (%A)†	29 ± 14#	38 ± 18#	51 ± 18
PT%C‡	64 ± 14.4**	51.1 ± 18	44.6 ± 19
WD_1 (mg)§	9 ± 2	8.9 ± 3	9.8 ± 2
WD_2 (mg)‖	7.4 ± 4	7.8 ± 2	9.1 ± 2
W (μ/mL) PT_3¶	0.85 ± 0.4	0.87 ± 0.36	1.02 ± 0.6
$PT_3 \geq 30$ seconds (N)	6	1	1
$PT_3 \geq 20$ seconds (N)	17	10	5

* PT_1 = baseline PT on 0600 the day warfarin is started.

† PT_3 = 16 hours after second warfarin dose.

$$‡\ PT\%C = \frac{PT_1\%A - PT_3\%A}{PT_1\%A} \times 100$$

§ WD_1 = warfarin dose, day one.

‖ WD_2 = warfarin dose, day two.

¶ Warfarin plasma levels obtained with PT_3.

# Cefamandole, cefazolin > vancomycin, $p < 0.05$.

** Cefamandole > cefazolin, vancomycin, $p < 0.01$.

The PT_1%A for the three groups was not significantly different ($p = 0.113$) (Table 2). PT_3%A was significantly lower for cefamandole and cefazolin, when compared with vancomycin, but not from one another. In contrast, the PT%C was significantly greater for cefamandole, compared with cefazolin and vancomycin, which were not significantly different. The first warfarin dose was ≥10 mg in 80% of patients receiving cefamandole, in 55% of patients receiving cefazolin, and in 85% of patients receiving vancomycin with the mean dose for each of the first two days and total dosage being similar. Warfarin plasma levels obtained with the PT_3 sample were not significantly different among the three groups. Cefamandole had a greater number of patients with PTs greater than both 20 and 30 seconds at PT_3 than the other two antibiotic groups.

The other identifiable difference between the three antibiotic groups was the relationship between the duration of postoperative prophylactic antibiotic therapy and the PT_1%A. Because the commencement of warfarin therapy was not controlled during this study, Table 3 lists the numbers of patients in each group who were receiving antibiotics concurrently when either PT_1, PT_2, or PT_3 was obtained. A linear regression using only those patients receiving antibiotics concurrent with the PT_1 sample compared the duration of antibiotics with the PT_1%A and indicated a moderate negative correlation for the cefamandole group ($R = -0.52$, $p = 0.05$) (Fig. 3), but not for cefazolin ($R = -0.16$, $p = 0.53$) or the vancomycin group ($R = -0.08$, $p = 0.82$). The mean duration of antibiotic therapy up to PT_1 was not significantly different among the three groups ($p = 0.12$).

TABLE 3. *The Number of Patients Receiving Concurrent Antibiotic Administration During the Time PT Samples Were Obtained and Average Duration of Antibiotic Therapy Until PT_1*

	Cefamandole N = 20	Cefazolin N = 20	Vancomycin N = 20
PT_1	15 (75)*	19 (95)	12 (60)
PT_2	14 (70)	11 (55)	8 (40)
PT_3	2 (10)	5 (25)	1 (5)
Therapy until PT_1 (days)†	4.6 ± 1.6	4.1 ± 0.8	3.8 ± 1.2

* N (% of total patients).

† Average number of days of antibiotic therapy until PT_1 obtained.

All of the PT_B%A values were greater than the patients' own PT_O%A. At least one of the PT_B%A values was equal or lower than the patients' PT_A%A in seven of nine patients (78%) who received cefamandole, in two of nine patients (22%) who received cefazolin, and in one of 12 patients (8%) who received vancomycin.

No bleeding episodes requiring transfusion were observed for the 60 patients. No apparent differences in outcome were associated with the three antibiotic groups and associated warfarin therapy.

Discussion

This prospective study reconfirms our previous retrospective report that patients receiving cefamandole, as a prophylactic antibiotic, had a greater hypoprothrombinemic response to warfarin than similar patients receiving vancomycin in the early postoperative period after prosthetic valve replacement. We reported previously that 14 of 44 patients (32%) receiving cefamandole and one of 16 patients (6%) receiving vancomycin had a $PT_3 > 32$ seconds, 16 hours after the second warfarin dose.[7] This is comparable to four of 20 (20%), 0 of 20, and 0 of 20 patients receiving cefamandole, cefazolin, and vancomycin, respectively, with a $PT_3 \geq 32$ seconds in the current study.

Although the PT%C supported a greater hypoprothrombinemia effect of cefamandole compared with cefazolin and vancomycin, we were surprised that the mean PT_3%A data were unable to differentiate statistically between cefamandole and cefazolin. This could be a result of too small of a sample size. The recent literature provides a possible explanation, but first we should review the three reported mechanisms of cephalosporin-induced hypoprothrombinemia.

The commonly cited mechanisms are[11]: (1) alteration of the bacterial bowel flora, with the suppression of vitamin K_1 production, (2) an inhibition of the carboxylation process necessary for the transformation of the procoagulant factors II, VII, IX, X to their active forms, and (3) the inhibition of vitamin K 2,3-epoxide reductase, which interferes with Vitamin K_1 activity.

The role of bowel flora in vitamin K production and its importance in maintaining a normal PT in humans is a subject of some dispute.[11] Most episodes of hypoprothrombinemia attributed to this mechanism have involved long-term, multiple antibiotic usage in seriously ill, malnourished, and potentially vitamin K-depleted patients or those with renal failure.[12] Our patients were not in renal failure; however, Blackburn et al. did report a 53% incidence of malnutrition in patients with a primary cardiac diagnosis. A subsample of 14 patients with valvular disease in NYHA Class III and IV were found to have a decreased weight/height index, skinfold thickness, and muscular circumference. Their patients' albumin levels, like ours, were generally within normal limits, but 10 of 14 patients tested negative for cell-mediated immunity.[13] We did not conduct a sophisticated nutrition assessment and cannot discount the possibility that an occult vitamin K deficiency existed, even with a normal PT_A before operation.

The pharmacologic basis for mechanisms 2 and 3 center on the MTT side chain found in not only cefamandole and several other cephalosporins (moxalactam, cefoperazone, cefotetan). Cephalosporins with the MTT side chain have been reported to cause hypoprothrombinemia more quickly and with greater frequency than non-MTT containing cephalosporins.[11] Lipsky reported that MTT inhibited gamma-carboxylation in a microsomal preparation prepared from rat livers.[14] Utolia and Suttie demonstrated that this inhibition was not due to the parent compound by reporting that cefamandole and structural analogs required much larger, and not clinically relevant, concentrations to produce 50% inhibition of the vitamin K-dependent carboxylase system.[15]

Vitamin K_1 2,3-epoxide reductase is found in the liver microsomes and reduces the vitamin K epoxide, formed from vitamin K_1 by carboxylase, back to the quinone or hydroquinone. Inhibition of vitamin K metabolism at the epoxide reductase step blocks the utilization of this vitamin. Bechtold et al. measured serum concentrations of vitamin K_1 2,3-epoxide, after giving 10 mg of vitamin K_1 intravenously in patients experiencing moxalactam- or cefamandole-induced hypoprothrombinemia. This metabolite is only measurable when vitamin K_1 is given in the presence of epoxide reductase inhibitors, such as coumarins or salicylates, and provides some inferential evidence that cefamandole has a coumarin-like action.[16]

None of the previous discussion would seem to support the possibility that cefazolin should have an additive hypoprothrombinemic effect with warfarin in our patient population. Kerremans et al. reported *in vitro* evidence that not only did MTT inhibit gamma-carboxylation but that MTD (2-methyl-1,3,4-thiadiazole-5-thiol), found in cefazolin, also had a similar effect.[17] They also demonstrated that the carboxylation inhibitory activity of both MTT and MTD was attenuated by methylation. Furthermore, MTD was a better substrate than MTT for both methylation enzymes: (1) thiopurine methyltransferase located in the kidney, and (2) thiomethyl transferase located in the liver. This could infer that MTD does not cause the same degree of hypoprothrombinemia because of rapid inactivation. However, MTD formation from cefazolin has not been demonstrated *in vivo.*[17]

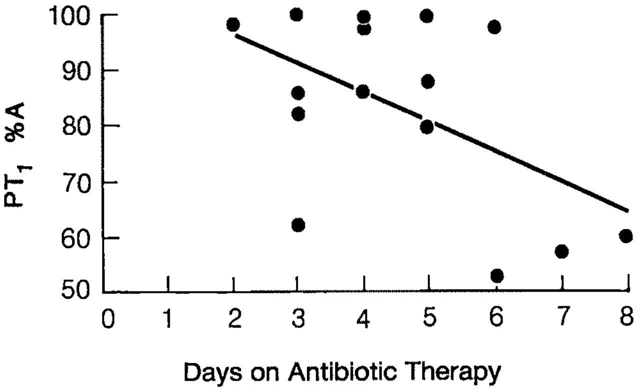

FIG. 3. The relationship between the duration of cefamandole administration and prothrombin per cent activity. The relationship between the double/double duration of prophylactic cefamandole therapy and the prothrombin time per cent activity on the morning that warfarin therapy was begun ($R = -0.52$, $p = 0.05$), indicating that as duration increased prothrombin activity declined.

Hypothermic cardiopulmonary bypass has influence on the entire clotting system. The vitamin K-dependent coagulation factors (II, VII, IX, X) have been reported to be depressed from 46% to 62% of preoperative values immediately after bypass.[18] This is consistent with our PT_O%A given in Table 1. Mori et al. measured the PT before operation and daily for 2 weeks after bypass surgery and reported that in only the first postoperative day PT, in seconds, was significantly greater than the preoperative PT. All PT values were within normal limits but the prophylactic antibiotic and its regimen were not specified.[19] A limited number of our patients in each group had two or three PT_B obtained and indicated a spontaneous recovery toward normal from the PT_O during the first 3–5 postoperative days. There is some hint that this return toward normal was inhibited in the cefamandole group by having more patients with a PT_B%A equal or less than their respective PT_A%A. In addition, there was a moderate correlation between an increasing duration of cefamandole therapy and decreased PT_1%A.

Although we did not attempt to quantitate the oral vitamin K intake of our patients after operation, the usual impression is that MTT-induced hypoprothrombinemia is quickly and easily reversed in a matter of hours by vitamin K administration.[11] This has not been universally true as Hooper et al.[5] and Fainstein et al.[20] reported. Lipsky provides experimental evidence that this MTT-induced hypoprothrombinemia may not be just a vitamin K inhibition problem because vitamin K_1 failed to reverse *in vitro* MTT inhibition of gamma-carboxylation after the reaction had started.[21] This may partially explain the low PT_1%A values that were noted in the cefamandole and cefazolin groups despite some oral food intake.

Yacobi et al. reported that 31 cardiovascular patients had total warfarin plasma levels of 0.4–3.27 μg/mL associated with a PT range of 15.6–29.8 seconds.[22] The warfarin plasma levels we obtained measured only the total racemic compound and were not at a steady state. Even so, they indicate that warfarin absorption took place, achieved similar concentrations, and are consistent with previous reported therapeutic concentrations in all three antibiotic groups.

The PT response to warfarin is influenced by many factors such as age, diet, congestive heart failure, or drug interactions to list a few. Sawyer et al. recently reported that age had a negative correlation with warfarin dosage requirements. This study included outpatients and a wider range of ages (19–91 years) than our patients.[23] The possible influence of the vancomycin group being 6–8 years younger on the PT response to warfarin in this setting is unknown. Yacobi et al. could find no rank order correlation between the average PT and average warfarin dose, total warfarin concentration, or free warfarin concentration.[22] The "normal" response to warfarin in the early postoperative phase in patients who had prosthetic valve replacement has not been rigorously documented to our knowledge; therefore, we cannot discount some other explanation for the observed differences among the three antibiotics. The consistent difference in PT response between cefamandole and vancomycin in this and our previous report, involving a total of 100 patients, supports a drug-induced effect.

The exact mechanism for the greater PT%C associated with the cefamandole group compared with cefazolin and vancomycin is unknown, but could possibly be due to the presence of MTT when the first warfarin doses were administered. The pharmacokinetics of MTT in this setting have not been reported and it is only recently that Aronoff et al. reported MTT disposition in a group of normal patients and in patients with anuric renal failure after a single intravenous dose of cefamandole. The patients with renal failure had a 10-fold increase in cefamandole half-life, and the MTT area under the curve was 50 times that seen in normals.[24] The importance of this is to the development of hypoprothrombinemia, or interaction with warfarin requires further study.

The possibility that the dosage regimens used for cefamandole and cefazolin were of unequal "PT suppression" potency cannot be discounted. We did not measure serum concentrations of either drug. Utolia and Suttie reported that cefamandole concentrations 10 times those observed after 2 g administered intravenously were needed to inhibit the vitamin K-dependent carboxylase system by 50%.[15] We were unable to find comparable data for cefazolin. Therefore, serum measurements of both parent compounds plus MTT and MTD would have to be done in an attempt to determine the relative "PT suppression" potency of these two cephalosporins.

Conclusion

This prospective study reconfirms our previous retrospective report that cefamandole can have an additive effect to warfarin in producing hypoprothrombinemia in the prosthetic heart valve patient. The study further provides evidence that cefazolin may have a similar, but intermediate, effect between cefamandole and vancomycin. Although none of our patients had an adverse reaction from this exaggerated hypoprothrombinemic response, we still recommend a baseline PT and caution before administering warfarin to patients receiving either cefamandole or cefazolin. The exact mechanism for this exaggerated hypoprothrombinemic response to warfarin after the administration of cefamandole or cefazolin is not completely understood but may be related to the MTT or MTD side chain and its influence on either gamma-carboxylation and/or vitamin K_1 2,3-epoxide reductase.

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Pulmonary Leukosequestration Induced by Hind Limb Ischemia

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Lower torso ischemia leads to acute respiratory failure, an event associated with the accumulation of inflammatory cells in the lungs. This study tests whether ischemia-induced eicosanoid synthesis leads to polymorphonuclear leukocyte (PMN) accumulation in the lungs. Anesthetized rats ($N = 51$) were randomized into five groups: nonischemic sham rats ($N = 10$); the remaining four groups were rats made ischemic for 4 hours with bilateral thigh tourniquets treated just before tourniquet release with saline vehicle ($N = 17$): the thromboxane (Tx) synthase inhibitor OKY-046 (Ono Pharmaceutica, Osaka, Japan) 2 mg/kg intravenously every 2 hours ($N = 8$); the lipoxygenase inhibitor diethylcarbamazine (DEC) (Sigma, St. Louis, MO) 0.2 mg/kg/min intravenously ($N = 8$); the platelet-activating factor receptor antagonist SRI (Sandoz Inc., East Hanover, NJ) 63-072 3 mg/kg intravenously every 30 minutes ($N = 8$). Four hours after ischemia, plasma TxB_2 levels in the ischemic placebo-treated group was 3570 ± 695 pg/mL, compared with 495 ± 73 pg/mL in sham rats ($p < 0.001$). Lung microscopy showed foci of proteinaceous exudate in alveoli and 121 ± 10 PMN/20 high power fields (HPF) compared with 59 ± 9 PMN/20 HPF in the sham group ($p < 0.001$). One day after ischemia PMN accumulations remained elevated at 119 PMN/20 HPF. Pretreatment with OKY-046 led to reduced TxB_2 levels of 149 ± 17 pg/mL, normal lung histology, and 83 ± 13 PMN/20 HPF, a value similar to that of the sham group and lower than that of the placebo-treated group ($p < 0.05$). Treatment with DEC yielded TxB_2 levels of 1419 ± 492 pg/mL, which was lower than that of the placebo group ($p < 0.05$) but higher than that of the sham group ($p < 0.05$). Microscopy showed normal lungs with 79 ± 7 PMN/20 HPF lower than the placebo group ($p < 0.05$). SRI 63-072 did not inhibit Tx synthesis or leukosequestration in the lungs. Platelet counts decreased in all groups relative to sham animals ($p < 0.05$). The results indicate that Tx synthesis induced by ischemia moderates PMN accumulations in the lungs. Inhibition of lipoxygenase is believed to prevent PMN accumulations both by limiting leukotriene-induced Tx synthesis as well as by limiting production of chemoattractants.

LOWER TORSO ISCHEMIA stimulates the release of a circulating agent(s), which leads to the accumulation of blood cells including polymorphonuclear leukocytes (PMN) in the lungs.[1,2] Neutrophil entrapment is considered to be the final event resulting in the local release of toxic agents and acute respiratory failure.[3]

Previous studies of ischemia have concluded that pulmonary injury occurs when blood cell microemboli are mechanically sieved by the lungs.[4] Since synthesis of the proaggregator and chemoattractant TxA_2 is stimulated by ischemia,[5] the current study was designed to test its role in blood cells, particularly neutrophil accumulations in the lungs. Further, the role of two other chemoattractants and activators of neutrophils, the leukotrienes (LT) and platelet-activating factor (PAF),[6-8] were included in the study to test their roles in pulmonary leukosequestration.

Methods

Fifty-seven male Sprague-Dawley rats (Charles River Breeding Laboratories, Wilmington, MA), weighing an average of 500 g, were anesthetized with 60 mg/kg of pentobarbital sodium administered by intraperitoneal injection. A jugular venous catheter was inserted for supplementary doses of anesthesia as well as fluid and drug administration. The volume of fluid given in all experiments was 2 mL/kg/h.

The animals were divided into five groups. In all animals, except the sham controls ($N = 10$), arterial tourniquets were applied to both thighs after a 2-minute elevation of the hind limbs to minimize the amount of retained blood. The animals were then placed prone, and after 4 hours the tourniquets were removed. Thirty minutes before tourniquet release, animals were randomized to receive: saline vehicle ($N = 23$); the thromboxane (Tx) synthase inhibitor OKY-046 (Ono Pharmaceutica, Osaka, Japan), 2 mg/kg by intravenous bolus, repeated every 2 hours ($N = 8$); the lypoxygenase

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inhibitor diethylcarbamazine (DEC)[9] (Sigma, St. Louis, MO), 0.2 mg/kg/min in a continuous intravenous infusion (N = 8); the platelet-activating factor (PAF) receptor antagonist SRI 63-072[10] (Sandoz Inc., East Hanover, NJ) in repeated intravenous boluses of 3 mg/kg every 30 minutes (N = 8). Treatment in all animals was continued for 4.5 hours when the experiment was ended.

After 4 hours of reperfusion, a midline laparotomy was performed and 5 mL of blood withdrawn from the inferior vena cava in syringes containing ethylene diamine tetracetic acid and aspirin. Platelets were counted by means of phase microscopy. The blood was then centrifuged at 1500 × g at 4 C for 20 minutes, the plasma separated and stored at −20 C until assayed. Plasma TxB_2 and 6-keto-$PGF_{1\alpha}$ were measured by radioimmunoassay.[11-13]

The rats were killed with intravenous potassium chloride, and the lungs harvested for light microscopy. This was done *via* a midsternotomy. Through a tracheostomy, gluteraldehyde was introduced into the lungs and kept under a constant hydrostatic pressure equivalent to a 20-cm column of water for 20 minutes. The trachea was then ligated, and the lungs removed and bathed in gluteraldehyde for 24 hours. Sections were taken from identical lung regions and were stained with hematoxylin and eosin. Leukocytes were counted in 20 high power fields (HPF). Sham control animals were studied (N = 10) where all procedures were done except the hind limbs were not made ischemic. Four animals of the sham group and three of the placebo-treated group were used to determine wet-to-dry lung weight ratios of the bloodless lung at the conclusion of the experiment, that is, after 4 hours of hind limb ischemia and 4 hours of reperfusion. Lastly, plasma TxB_2 levels, lung weights, and PMN entrapment were assayed in placebo-treated rats 24 hours (N = 3) and 48 hours (N = 3) after ischemia.

Results are presented as the mean ± SE. Significance between means was tested by an analysis of variance and nonpaired t-test. Significance was accepted if $p < 0.05$.

Animals used in this study were maintained in accordance with the guidelines of the Committee of Animals of the Harvard Medical School and those prepared by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources, National Research Council (DHEW publication no. [NIH] 78-23, revised 1978).

Results

Four hours of reperfusion after a 4-hour period of hind limb ischemia resulted in a rise of plasma TxB_2 in the placebo-treated animals to 3579 ± 695 pg/mL, compared with 495 ± 73 pg/mL in the nonischemic sham group ($p < 0.001$) (Fig. 1). There was also a rise in 6-keto-$PGF_{1\alpha}$ to 285 ± 50 pg/mL compared with sham treatment values of 156 ± 50 pg/mL ($p < 0.05$) (Fig. 2).

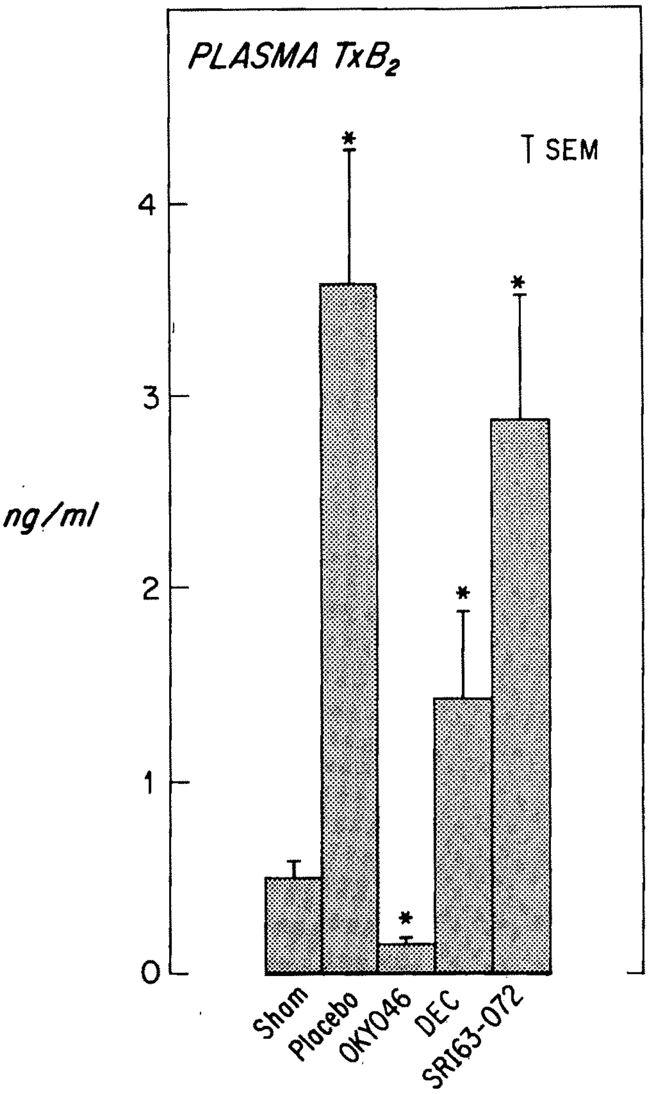

FIG. 1. Four hours of reperfusion after bilateral hind limb ischemia led to a rise in plasma TxB_2 levels compared with those of sham animals. OKY-046 prevented this phenomenon, whereas DEC modified it. The PAF antagonist, SRI 63-072, was without effect. Asterisks refer to significant differences between the sham group and other groups.

Microscopic examination of the lungs of sham animals showed normal histologic features (Fig. 3), whereas placebo-treated ischemic animals demonstrated accumulations of PMNs in the capillary beds throughout the lung parenchyma (Fig. 4). Most neutrophils were contained within vessels, but foci of inflammatory cells and proteinaceous exudate within alveolar air spaces were also present. The accumulation of PMNs in the lungs was in excess of what could be attributed to local differ-

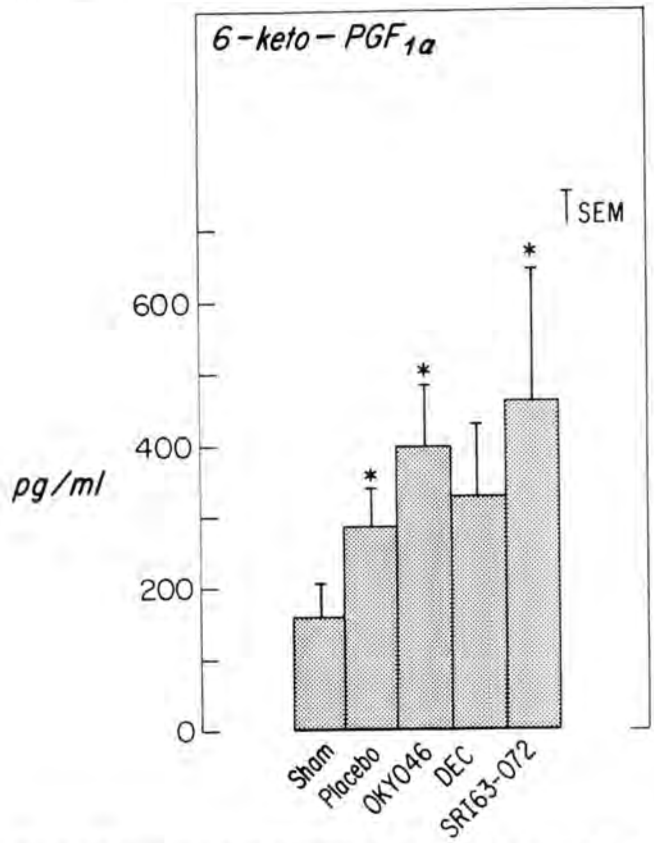

FIG. 2. After ischemia there was an increase in plasma 6-keto-$PGF_{1\alpha}$ in all groups compared with the sham group, although the rise in the DEC group was not significant. Asterisks refer to significant differences between the sham group and other groups.

ences in blood volume or vascular congestion. Quantitative counts of PMN in the lungs were 121 ± 10 PMN/20 HPF, higher than the sham group value of 59 ± 9 PMN/20 HPF ($p < 0.001$) (Fig. 5). Wet-to-dry weight ratios of the lungs in placebo-treated and sham groups were 4.97 ± 0.24 and 4.89 ± 0.05, respectively.

Pretreatment with OKY-046 blocked ischemia induced TxB_2 synthesis. After 4 hours of reperfusion, TxB_2 levels were 149 ± 17 pg/mL, lower than the sham group ($p < 0.001$). Few abnormalities were noted on microscopy. Accumulation of neutrophils was 83 ± 13 PMN/20 HPF, similar to that of the sham group and reduced compared with that of placebo-treated animals ($p < 0.05$) (Fig. 5). In the DEC-treated group, TxB_2 levels were 1419 ± 492 pg/mL, a value higher than that of sham animals ($p < 0.05$) but lower than that of the placebo-treated group ($p < 0.05$) (Fig. 1). Histologic features of the lungs were virtually normal, and leukocyte count in the lungs was 79 ± 7 PMN/20 HPF (Fig. 5), lower than that of the placebo-treated group ($p < 0.05$). The PAF antagonist, SRI 63-072, had no significant effect on TxB_2 levels, 2912 ± 635 pg/mL, nor on leukosequestration in the lungs, 110 ± 26 PMN/20 HPF, both measurements being higher than levels in sham animals and similar to levels in placebo-treated animals.

Platelet counts decreased significantly in all four ischemic groups compared with that of sham animals ($p < 0.05$) (Fig. 6). Platelet aggregates were not seen in histologic sections.

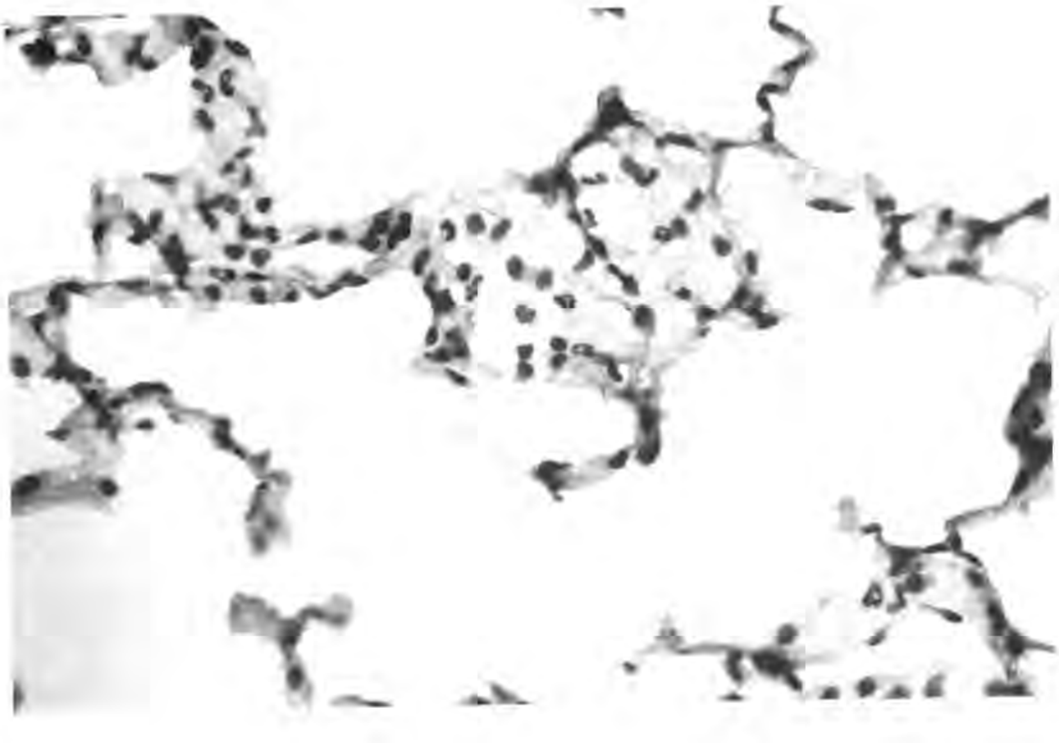

FIG. 3. Histologic specimens of the lungs in placebo-treated animals showed accumulations of PMNs in the capillary bed, mostly within vessels. Occasionally, foci of inflammatory cells and proteinaceous exudate were present within alveolar air spaces as seen in the central portion of the figure.

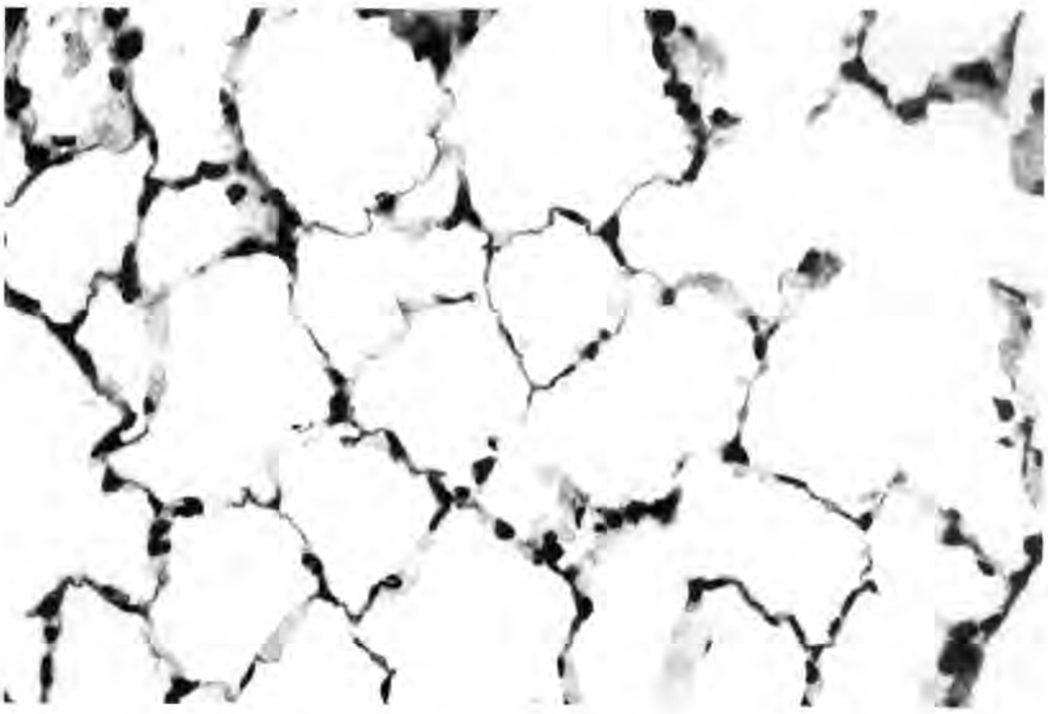

FIG. 4. The histologic features of lungs of sham animals were normal.

Placebo-treated animals that were studied 24 hours after release of the thigh tourniquets had normal TxB_2 levels of 436 ± 105 pg/mL but lung leukocyte counts were still high at 119 ± 1 PMN/20 HPF. After 48 hours, TxB_2 levels were 763 ± 118 pg/mL and lung leukocyte counts were 94 ± 6 PMN/20 HPF.

Discussion

Reperfusion after a 4-hour ischemic stimulus led to a prominent rise in plasma TxB_2, which returned to baseline after 24 hours. Similar findings have been noted in dogs after application of a thigh tourniquet and in humans after abdominal aortic cross-clamping during aneurysm surgery.[5,14] Associated with this rise in TxB_2 was an accumulation of leukocytes in the lungs (Fig. 5) that cleared slowly, over the next 2 days. Although there was no increase in the wet-to-dry weight ratio 4 hours after ischemia when PMN accumulations were prominent, there was histologic evidence of microvascular injury manifest by focal proteinaceous exudate into alveolar air spaces (Fig. 3). Previous observations of the pulmonary consequences of lower torso ischemia have documented blood cell accumulations in the lungs, believed to be due to embolization of microaggregates from the ischemic legs.[1,2,4] That platelet counts were noted to fall during neutrophil sequestration in the lungs (Fig. 6) is consistent with the formation and embolization of platelet microemboli. However, histologic observations make this unlikely. Platelet aggregates were not noted by lung microscopy in animals who had PMN accumulations (Fig. 3). Secondly, pharmacologic inhibition of Tx and LT was successful, at least in part, in preventing the PMN accumulations in the lungs but not the decline in circulating platelet numbers (Figs. 5 and 6). It is unlikely that the proaggregators being inhibited, that is TxA_2, would selectively aggregate PMNs and not platelets.

That mechanical filtration of PMN aggregates by the lungs is unlikely makes plausible the thesis that agents such as TxA_2 and LTB_4 lead to pulmonary endothelial–neutrophil interactions.[15] Adherence of PMN to pulmonary endothelium is a necessary initial step. It is possible that LTB_4 acts principally on endothelium.[16] LTB_4-stimulated Tx synthesis by endothelium, an event recently described,[17] may be a critical intermediary step. Thus, LTB_4 when applied to abraided skin or when injected subcutaneously will lead to the local generation of Tx and PMN accumulations, events that can be prevented with Tx synthase antagonists.[18] In other settings where Tx synthesis is stimulated, such as in experimental acid aspiration, PMN accumulations in the lungs are noted.[19] This can be limited by inhibition of Tx synthesis. The precise mechanism of TxA_2 action in these settings is unknown but is believed to involve endothelial–PMN adherence.

It is also theorized that thromboxane may act directly on actin filaments in endothelium in a manner similar

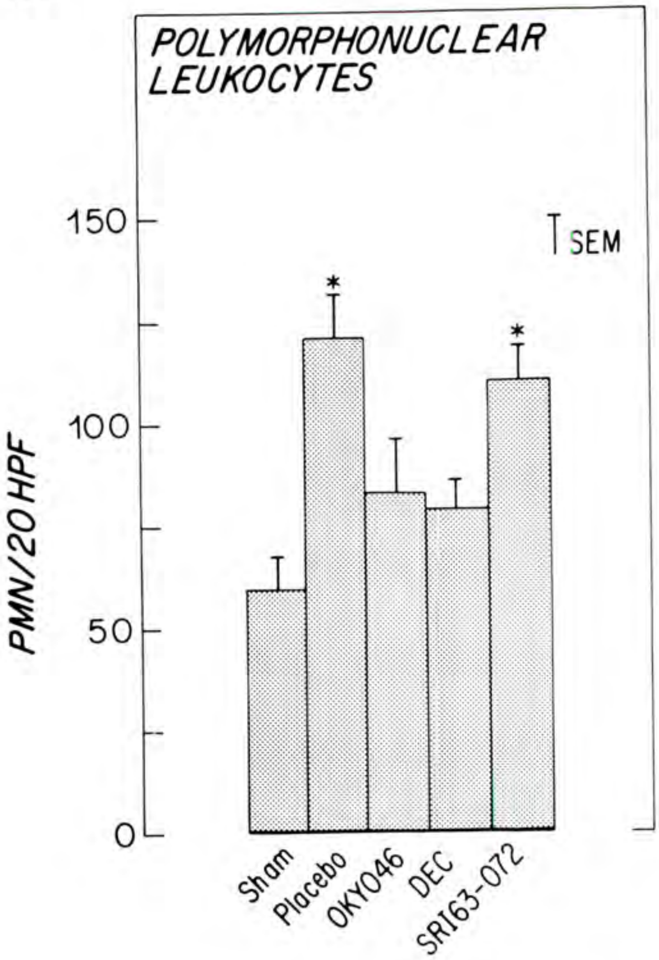

FIG. 5. Leukocyte entrapment was greater in placebo-treated animals than in the sham group. Pretreatment with OKY-046 and DEC significantly reduced pulmonary leukosequestration. Asterisks refer to significant differences between sham-treated animals and other groups.

to vasoactive amines to encourage PMN movement out of the microvasculature by diapedesis.[20] Actin filaments are believed to be important determinants of the size of intercellular clefts between endothelial cells. The opening of these tight junctions occurs when the actin cables are disassembled by agents such as histamine, LTB_4, and TxA_2.[21] This leads to increased permeability to macromolecules as well as to increased PMN diapedesis.[20,22]

The observation that treatment with DEC leads to a lowering of TxB_2 levels may be due to inhibition of LT and LT-induced generation of Tx.[17] The salutory effect of DEC on PMN accumulations may be due both to this reduction in TxA_2 as well as to a decrease in synthesis of the chemoattractant LTB_4. Both eicosanoids may contribute to leukosequestration by moderating the size of gap junctions as well as PMN–endothelial interactions.

The inability of the PAF antagonist SRI 63-072 to alter PMN accumulations was a surprise. We interpret the results to indicate that PAF is not released as a consequence of ischemia. In further support of this thesis, had PAF been released, circulating blood cells should have been stimulated to synthesize TxA_2.[23] Inhibition of PAF should then have led to a fall in plasma TxB_2, which did not occur.

Other agents, particularly the complement fragment C5a, are not likely to mediate ischemia-induced leukosequestration in the lungs. In a previous study, Tx inhibitors could not prevent PMN accumulations resulting from the intravenous injection of zymosan-activated plasma, a source of C5a. The vasodilating, antiaggregating prostaglandins (PG), such as PG_2, are also not likely to be involved. Levels of 6-keto-$PGF_{1\alpha}$ did not predict PMN accumulations nor did the PG/Tx ratio.

In summary, these results indicate that limb ischemia leads to Tx synthesis and PMN accumulations in the lungs, events that appear to be causally related.

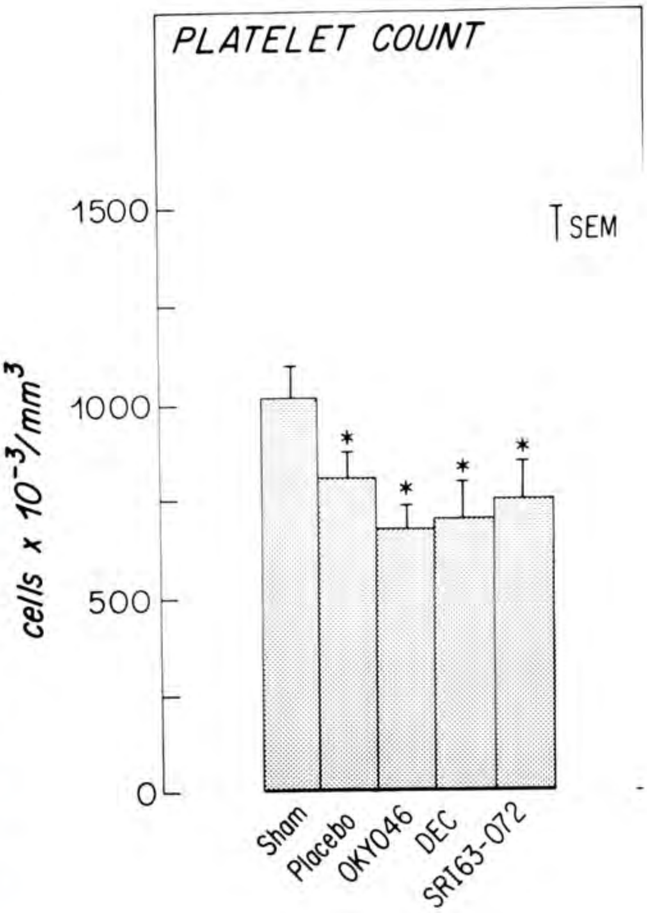

FIG. 6. Platelet counts fell in all ischemic groups. Asterisks refer t significant differences between the sham group and other groups.

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Reoperation for Femoral Anastomotic False Aneurysm

A 15-year Experience

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An experience on the surgical treatment of anastomotic false aneurysms during the last 15 years was reviewed. Fifty-nine were femoral anastomoses complicated by false aneurysm appearance requiring surgical excision. They represented 2.9% of all femoral anastomoses performed, whereas they represented 3.3% when considering reconstruction in which the femoral artery was the distal anastomosis. Reconstructions with distal anastomosis performed on the femoral artery were primarily involved (58 of 59), whereas grafts with "take off" from the femoral artery were rarely affected ($p < 0.05$). A higher incidence of false aneurysm formation was demonstrated in hypertensive patients ($p < 0.05$) as well as those who previously had femoral thromboendarterectomy ($p < 0.01$). Infection was considered a causative factor even if it developed before (6–14 months) false aneurysm appearance. When a false aneurysm was resected, the best hemodynamic reconstruction, to avoid recurrence, was considered a bypass with distal anastomosis performed end-to-end on the femoral artery ($p < 0.05$). The surgical treatment of choice was false aneurysm resection and graft interposition. However, a reanastomosis in the presence of small false aneurysms, when technically possible, has been successfully performed. Both treatments allowed good long-term results.

THE INTRODUCTION OF vascular grafts almost 30 years ago helped surgeons to solve many important vascular problems. Efforts since that time have been made to improve the quality of graft materials and their results. Better prostheses have been developed since that time with great improvement in the results. Nevertheless, graft implantation is still complicated by two major problems: the occurrence of anastomotic false aneurysms and infection. The first complication is common in the groin and currently constitutes an unsolved puzzle. Much work has been done to focus on the major factors influencing this vascular complication. The first imputed was the type of suture used to complete the anastomosis.[1-3] However, femoral false aneurysms continue to occur despite the abandonment of silk and braided Dacron as suture materials.[4,5] Infection, hypertension, tension of a graft, local thromboendarterectomy, and turbulance at the anastomotic site have also been considered as factors in many qualified reports.[4,6] However, it has not been clearly demonstrated that all of these factors are present more frequently in patients in whom false aneurysms developed than in patients in whom they do not. To clarify some of these etiologic factors, we present the experience of our group during the last 15 years.

Materials and Results

From 1971 through 1985, we have treated, by means of vascular reconstruction, a total of 2053 femoral sites in 1169 cases. The type of reconstruction performed is reported in Table 1. Sixty-six were femoral anastomoses complicated by an anastomotic aneurysm that required surgical excision (>3 cm): 59 (2.9%) were anastomotic false aneurysms, whereas the other seven were true aneurysms and were, therefore, excluded from this study. Thirty of the affected patients (24 men and 6 women) had a mean age of 66.4 years (SD ± 8.2), median age was 66 years. Forty-eight femoral sites were involved, and 11 were recurrent. Eighteen patients were bilaterally affected. Associated pathologic conditions are reported in Table 2.

All patients had extensive vascular disease with 80% having had a minimum of three vascular procedures (mean: 5.4). The diagnosis was always "clinical" (Fig. 1A). Angiography was limited to cases in which distal obstructive lesions or multiple false aneurysms were suspected (Fig. 2). All false aneurysms developed at the

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TABLE 1. *Reconstructions Involving the Femoral Site Considered at Risk for False Aneurysm Development*

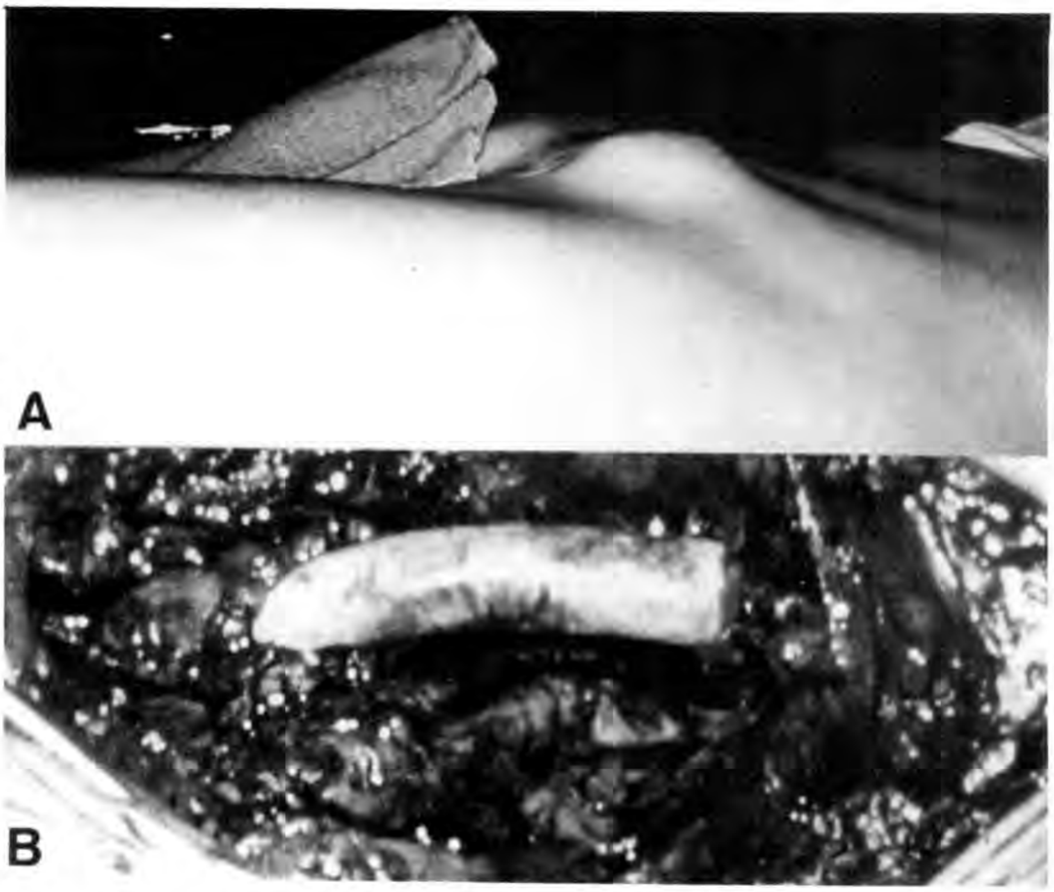
	No. of Cases	Femoral Anastomoses
Aortofemoral (aneurysm)	489	978
Aortofemoral (obstructive disease)	366	732
Femoropopliteal	184	184
Femorotibial	36	36
Axillofemoral	7	7
Femorofemoral	29	58
Thoracofemoral	15	15
Iliofemoral	43	43
Total	1169	2053

TABLE 2. *Patients Profile**

Age (years)	66.4 ±8.2
Sex (M:F)	24:6
Smoking	27 (90)
Hypertension	18 (63.3)
Previous MI by history and/or ECG	10 (33.3)
Chronic pulmonary obstructive disease	11 (36.6)
Cerebrovascular insufficiency	8 (26.7)

* ( ) percentages.
MI = myocardial infarction.

anastomosis between an aorto-, thoraco-, or femorofemoral graft and the femoral artery (distal anastomosis) except one, which appeared at the anastomosis between a femoropopliteal bypass and one limb of the previous aortofemoral reconstruction (proximal anastomosis). Thirteen patients were previously operated on for an abdominal aortic aneurysm and had 26 femoral false aneurysms (4 recurrences) develop. Seventeen patients were operated on for obstructive disease and had 33 false aneurysms (7 recurrences) develop. The surgical procedure consisted of an aneurysmectomy and graft reanastomosis in 14 (23.7%) patients. Although a local graft interposition was performed in 43 (72.9%) patients, in two (3.4%) patients, the entire aortofemoral reconstruction had been replaced due to a concommitant false aneurysm at the aortic site. The distal anastomosis of this reconstruction was performed end-to-end in 31 (52.5%) patients (Fig. 1B) and end-to-side in 11 (18.7%) patients. In one (1.7%) patient, we could not precisely indicate the type of distal anastomosis (Fig. 3). The sutures used to perform the anastomosis complicated by false aneurysm formation are shown in Table 3. Reoperation for false aneurysm was performed after a mean of 58.4 months (SD ± 28.7) from the previous vascular procedure. Recurrence of false aneurysm appeared after a mean of 30.1 months (SD ± 25.8) after the first repair.



FIGS. 1A and 1B. *A.* Patient affected by an anastomotic femoral false aneurysm. *B.* Intraoperative image of the PTFE graft used for repair. Both anastomoses were performed end-to-end.

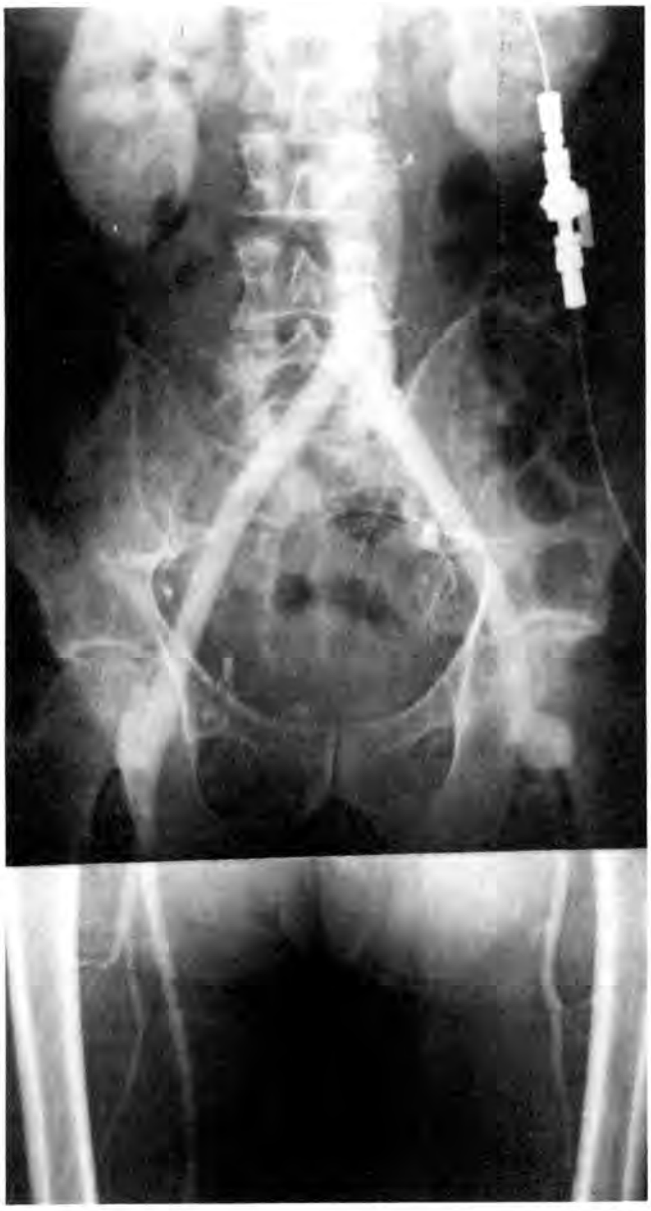


FIG. 2. Angiography of patient affected by an anastomotic femoral false aneurysm. Occlusion of left superficial femoral artery is shown, with complaints of related symptoms.

A previous femoral thromboendarterectomy was performed on a total of 26 (44.2%) patients. This procedure was primarily performed in patients treated for occlusive disease (18 of 33), whereas in abdominal aneurysms it was more infrequent (8 of 26).

Infection was considered a factor in seven cases; however, only two cases presented with a clinical infection and positive culture at the time of false aneurysm repair; whereas in five cases infection had been present before the repair (6–14 months). Cultures were always obtained and showed a negative result in all false aneurysms, except in the two cases with clear clinical infection.

Antibiotics were routinely used for 5–7 days after surgery.

The follow-up results showed an incidence of recurrence in patients treated by simple reanastomosis similar to the group treated by graft interposition: 21.4% and

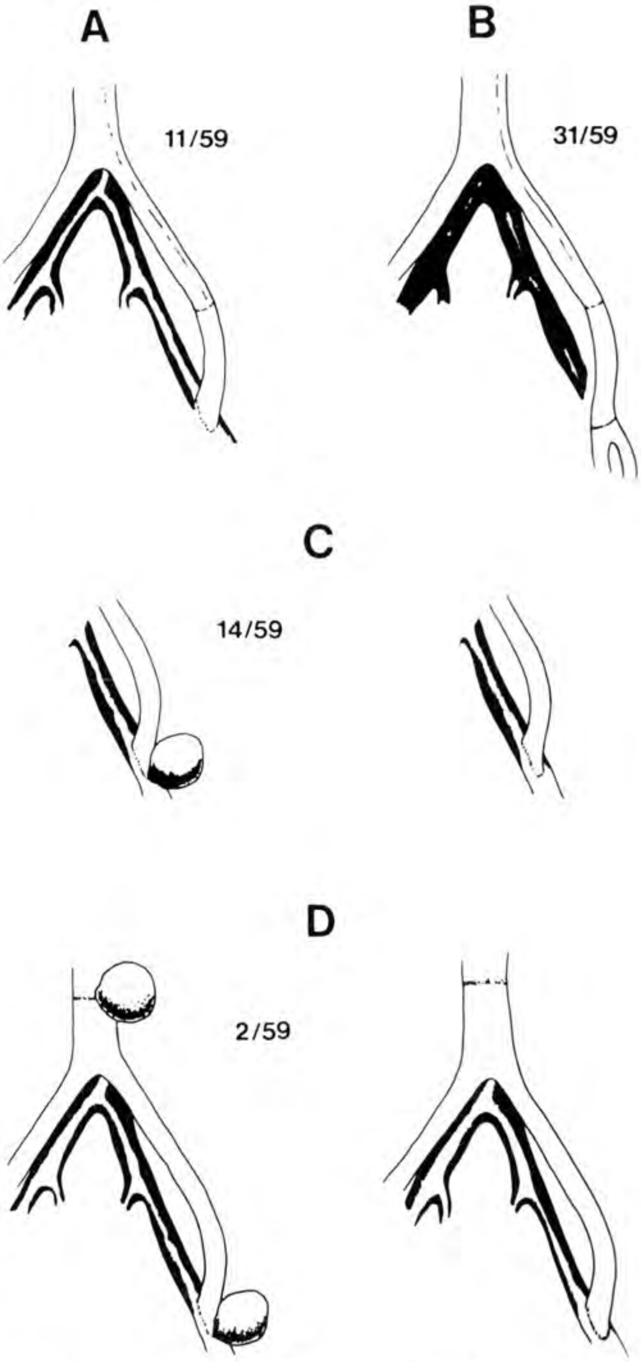


FIG. 3. Surgical procedures. One case treated by graft interposition has not been included because we could not clarify the type of distal anastomosis performed. Another case involved a venous femoropopliteal artery bypass and has been included in Group A. The treatment consisted of resecting the distal portion of the aortofemoral graft with graft (PTFE) interposition (end-to-end) and reanastomosis of the vein femoropopliteal bypass to this new graft.

17.5%, respectively (NS). In both groups, long-term results were successful (Table 4).

Discussion

Several different factors became evident concerning anastomotic false aneurysm. The femoral site is surely more affected than others. From the statistical analysis of our data, we can easily confirm that femoral false aneurysm is a complication of reconstruction with distal anastomosis performed on the femoral artery. False aneurysm development is rarely a problem when the femoral anastomosis represents the proximal part of the reconstructive procedure, 1:58 ($p < 0.05$). The etiology of this complication is multifactorial. The incident percentage has been reported to range between 2 and 5% in different reports.[1-10] In our series, the incidence was 2.9%, but if we consider only those reconstructions with distal anastomoses performed on the femoral artery, it increases to 3.3%. Great emphasis was given to the type of prosthesis and suture used to perform the original reconstruction. Undoubtedly, these are factors that may influence the development of false aneurysms. Cutler and Dunphy[11] demonstrated fragmentation of silk fibers and removal of fragments by phagocytes years ago. However, the great progress that has been done to improve the quality of suture and graft material has been widely reported as a cause of reduction in false aneurysm formation due to suture destruction or graft dilation. In the past, these two factors were reported with more emphasis than now.[8,9] To reinforce this hypothesis, Dennis et al.[4] emphasized how, in more recent reports, the time between the original operation and the false aneurysm appearance is longer (6.2 years) than in the past. This latter data are confirmed in our series (58.4 months); however, in our opinion, due to the long mean time of appearance of this complication, a definitive opinion on these factors can be given only after certain years because of the relatively recent introduction of monofilament sutures (1982 in our series).

Progressive arteriosclerotic deterioration of the femoral artery played a great role. Therefore, the quality of the host arterial wall is extremely important to preserve the anastomosis. Local thromboendarterectomy at this site with related weakening of the arterial wall and subsequent false aneurysm formation has already been described.[1,7,10] In our patients, this hypothesis was proved and was extremely important if we consider separately the patients operated on for aneurysm and for obstructive disease. The number of previous thromboendarterectomies in this last group was significantly higher compared with the number of thromboendarterectomies performed in our series during similar vascular reconstruction of the femoral artery not complicated by femoral false aneurysm (34.1%) ($p < 0.01$).

TABLE 3. *Sutures Used to Perform the Anastomosis Complicated by False Aneurysm*

	N
Braided Dacron	31
Brain polyester	22
Polypropylene	2
Silk	1
Unknown	3

In our series, a clear-cut clinical infection with positive cultures at the site of false aneurysm repair was rarely present (2 cases/1 patient). These two cases were successfully treated by means of excision of the infected aortofemoral graft with saphenous vein reconstruction to each femoral area with a proximal and distal anastomosis as far distal as possible from the infected area. Antibiotics were used for 15 days after surgery, and the patient had no recurrence of infection (follow-up: 53 months).

Nevertheless, infection was considered a factor in seven (11.9%) of our cases. In five cases, false aneurysm developed 6–14 months after a graft infection (Szilagyi, grade 3). These five cases were treated by means of complete or partial excision of the infected graft and new vascular reconstruction. False aneurysm of this reconstruction site was considered to be related to a previous infection due to the same localization and relatively short time of developing, even though cultures were always negative. In Table 5 we present the removed infected grafts, their culture, and the new reconstruction complicated later by false aneurysm appearance and its follow-up. In our opinion, infection can be considered

TABLE 4. *Follow-up (Mean: 42.1 months)*

	No. of Patients (%)				
	Alive	Dead	Amputated	Postoperative Mortality	Recurrence
Reanastomosis (N = 14)	6 (42.9)	3 (21.4) 9 (64.3)	0	2 (14.3)	3 (21.4)
Reconstruction (N = 45), (5 lost to follow-up)	28 (70)	2 (5) 32 (80)	2 (5)	1 (2.5)	7 (17.5)

TABLE 5. *False Aneurysm Developing in Graft Treated Operatively for Infection*

Removed Infected Graft	Culture	New Reconstruction	False Aneurysm Development (months)	Follow-up
Aortobifemoral	No growth	Thoracofemoral + femorofemoral	12	Patent after 60 months
Aortobifemoral	No growth	Thoracofemoral + femorofemoral	12	Patent after 60 months
Aortobifemoral	*S. aureus*	Thoracofemoral + femorofemoral	14	Graft occlusion at 26 months, rest pain, no evidence of infection
Aortobifemoral	*S. aureus*	Thoracofemoral + femorofemoral	14	Graft occlusion at 26 months, rest pain, no evidence of infection
Aorto-left femoral	*S. epidermidis*	Left stump to Left femoral	6	Infection recurrence; amputation and death at 30 months

an important but infrequent risk factor in the development of false aneurysm, which deserves long-term follow-up study.

In our series, hypertension was present in a significantly higher range (63.3%) than in the atherosclerotic population ($p < 0.05$) and can, therefore, be considered a risk factor.

Among the mechanical factors, we believe that the high difference of compliance between the prosthesis and the femoral artery is surely an important cause of stress of the anastomotic site. In a previous study,[12] our senior author (R.D.S.) demonstrated that the difference in resilience of diseased femoral arteries and prosthetic material can be 15 times superior. Moreover, the turbulence at the anastomotic site caused by the end-to-side anastomosis can submit the host artery to relatively high stress that easily can be related to the false aneurysm formation.

In our opinion, end-to-end anastomosis, if possible, should always be performed for a false aneurysm repair to minimize the turbulence caused by the end-to-side anastomosis and, therefore, avoid a recurrence. In our series, the false aneurysm recurrences appear in a higher incidence, 3:1, ($p < 0.05$) after an end-to-side reconstruction or reanastomosis compared with the end-to-end anastomosis. To minimize turbulent effects at the anastomotic site, Szilagyi et al.[6] suggested to perform the end-to-side anastomosis with a very small angle (30°). This helpful criteria should always be followed for aortofemoral reconstruction, but only as a second choice to repair a false aneurysm, when an end-to-end anastomosis is not possible.

Resection of false aneurysm and reconstruction with graft interposition provides good long-term results. Simple reanastomosis can also be performed with success in small false aneurysms and/or when technically possible. If the false aneurysm is infected, the graft should be removed and another vascular reconstruction performed as far distant as possible from the infected site. When a false aneurysm also involves the aortic site, a complete removal of the aortofemoral graft is the treatment of choice. Reviewing our 59 cases during the past 15 years, we can make the following conclusions: (1) femoral false aneurysm formation is an important, although infrequent, complication of arterial reconstructions with distal anastomosis on the femoral artery; (2) local thromboendarterectomy should be avoided at the femoral site when possible because it represents a factor of false aneurysm formation; (3) end-to-end anastomosis at the femoral site reduces the risk of false aneurysm development due to its better hemodynamics; (4) infection is a causative factor even if it develops before (6–14 months) the false aneurysm appearance; and (5) treatment of choice is a graft interposition, but also a reanastomosis can be successfully performed. Both treatments allow good long-term results.

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3. In controlled studies in normal volunteers, elevations in SGPT have been observed when H_2-antagonists have been administered intravenously at greater than recommended doses for five days or longer. Therefore, it seems prudent in patients receiving IV ranitidine at doses greater than or equal to 100 mg qid for periods of five days or longer to monitor SGPT daily (from day 5) for the remainder of IV therapy.

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In normal volunteers, SGPT values were increased to at least twice the pretreatment levels in 6 of 12 subjects receiving 100 mg qid IV for seven days, and in 4 of 24 subjects receiving 50 mg qid for five days. With oral administration there have been occasional reports of reversible hepatitis, hepatocellular or hepatocanalicular or mixed, with or without jaundice.

Reversible blood count changes (leukopenia, granulocytopenia, and thrombocytopenia) have occurred in a few patients. Rare cases of agranulocytosis or of pancytopenia, sometimes with marrow hypoplasia, have been reported.

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PRECAUTIONS: General: Consult the absorbable gelatin sponge product labeling for complete information for use prior to utilizing the thrombin-saturated-sponge procedure.

Pregnancy—Teratogenic effects: Pregnancy Category C. Animal reproduction studies have not been conducted with Thrombin, Topical (Bovine). It is also not known whether Thrombin, Topical (Bovine) can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Thrombin, Topical (Bovine) should be given to a pregnant woman only if clearly indicated.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: An allergic type reaction following the use of Thrombostat for treatment of epistaxis has been reported. Febrile reactions have also been observed following the use of Thrombostat in certain surgical procedures but no cause-effect relationship has been established.

DOSAGE AND ADMINISTRATION: General: Solutions of Thrombostat may be prepared in sterile distilled water or isotonic saline. The intended use determines the strength of the solution to prepare. For general use in plastic surgery, dental extractions, skin grafting, neurosurgery, etc, solutions containing approximately 100 units per ml are frequently used. For this, 10 ml of diluent added to the 1000 unit package is suitable. Where bleeding is profuse, as from cut surfaces of liver and spleen, concentrations as high as 1000 to 2000 units per ml may be required. For this the 5000 unit vial dissolved in 5 ml or 2.5 ml respectively, of the diluent supplied in the package is convenient. Intermediate strengths to suit the needs of the case may be prepared by selecting the proper strength package and dissolving the contents in an appropriate volume of diluent. In many situations, it may be advantageous to use Thrombostat (Thrombin, USP) in dry form on oozing surfaces.

Caution: Solutions should be used the day they are prepared. The solution may be used for up to 6 hours when stored at room temperature; up to 24 hours when stored under refrigeration, and, if necessary, up to 48 hours when stored frozen.

The following techniques are suggested for the topical application of Thrombostat.

1. The recipient surface should be sponged (not wiped) free of blood before Thrombostat is applied.
2. A spray may be used or the surface may be flooded using a sterile syringe and small gauge needle. The most effective hemostasis results when the Thrombostat mixes freely with the blood as soon as it reaches the surface.
3. In instances where Thrombostat in dry form is needed, the vial is opened by removing the metal ring by flipping up the plastic cap and tearing counterclockwise. The rubber-diaphragm cap may be easily removed and the dried Thrombostat is then broken up into a powder by means of a sterile glass rod or other suitable sterile instrument.
4. Sponging of treated surfaces should be avoided in order that the clot remain securely in place.

Thrombostat may be used in conjunction with Absorbable Gelatin Sponge, USP as follows:

1. Prepare Thrombostat solution of the desired strength.
2. Immerse sponge strips of the desired size in the Thrombostat solution. Knead the sponge strips vigorously with moistened gloved fingers to remove trapped air, thereby facilitating saturation of the sponge.
3. Apply saturated sponge to bleeding area. Hold in place for 10 to 15 seconds with a pledget of cotton or a small gauze sponge.

Thrombostat Kit: Thrombostat Kit contains one sterile 20,000 unit vial of Thrombostat, one sterile vial of Isotonic Saline Diluent, and one sterile pump sprayer cap. The Kit may be used as follows:

1. Remove the Tyvek blister lid by pulling up at the indicated corner. The sterile inner tray can be lifted out or introduced into the operating field.
2. The cover to the sterile inner tray is removed by pulling up on the finger tab, exposing the sterile contents.
3. Thrombostat solution of the desired strength is prepared and the pump sprayer cap inserted and seated on the Thrombostat solution vial. Note: Several strokes of the pump sprayer will be required before the Thrombostat solution is expelled.
4. Alternatively, when Thrombostat in dry form is needed, the vial is opened as described above and the dried Thrombostat broken up into a powder by means of a sterile glass rod or other suitable sterile instrument.

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For asymptomatic persons the Society recommends annual digital rectal examination at age 40 and over; at age 50 and over, an annual stool blood test, as well as sigmoidoscopy every three to five years, following two initial annual negative sigmoidoscopies.

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*"Cancer of the Colon and Rectum: Summary of Public Attitude Survey," *Ca* 33:359-365, 1983 (Nov.-Dec.).

Drug-induced Esophageal Strictures

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A retrospective study of 55 patients with a benign esophageal stricture showed that in 11 patients (20%) the cause was a drug-induced lesion due to potassium chloride (3), tetracyclines (3), aspirin (2), vitamin C (1), phenytoin (1), and quinidine (1). Five of the 11 patients would have been diagnosed as having a reflux etiology of their stricture if 24-hour esophageal pH monitoring was not performed. Six patients responded to dilatation and five patients required resection or bypass. A prospective study of 18 asymptomatic volunteers showed a high incidence of esophageal lodgment of a radiolabeled medicinal capsule, with subsequent dissolution and release of the isotope. This occurred most frequently in elderly subjects and was reduced by increasing the volume of water chaser. The sites of lodgment correspond to the location of the observed strictures in the patient population. An *in vitro* study showed that, when the causative drugs were mixed with saliva, dissolution occurred within 60 minutes and was associated with significant changes in pH. These investigations show that drug-induced esophageal strictures are more common than previously appreciated, and can be confused with a reflux etiology. Diagnosis is suggested by a history of drug ingestion, location of the stricture, and a normal esophageal acid exposure on 24-hour pH monitoring. The severity of the esophageal injury is variable and requires dilatation to resection for therapy.

WITH THE INTRODUCTION of the 24-hour esophageal pH monitoring test into clinical practice it became evident that some patients, suspected to have a reflux stricture, did not show an increased esophageal acid exposure after dilation.[1] Because an understanding of pathogenesis is important for appropriate therapy, this finding stimulated the search for causes of stricture formation other than gastroesophageal reflux. In this search, two important observations were made from the literature. First, the number of reported esophageal injuries due to the ingestion of commercially available medications has steadily increased over the past 15 years.[2,3] Second, the ulcerogenic potential of several drugs on the esophageal mucosa has been demonstrated in animal models.[4,5] The purpose of this study was: (1) to establish the prevalence of drug-induced esophageal strictures in patients referred for surgical therapy, and (2) to investigate the pathophysiology of a drug-induced esophageal lesion.

Retrospective Clinical Study

Studied Population

From 1973 to 1986, 55 patients were referred to one of the authors (TRD) for treatment of a benign esophageal stricture. There were 30 men and 25 women, with a mean age of 57 years, ranging from 17 to 86 years. All patients complained of dysphagia and showed an esophageal stricture on roentgenographic barium study. Flexible esophagoscopy with multiple biopsies and brushing of the stricture was performed in all patients. When the stenosis appeared suspicious for malignancy and the initial biopsy showed a benign lesion, a more adequate biopsy specimen was obtained to exclude malignancy using the rigid esophagoscope. All biopsies showed esophagitis or fibrosis, and five patients had an associated Barrett's esophagus. Esophageal manometry and 24-hour pH monitoring were performed in patients whose strictures were successfully dilated up to a 60 French bougie.

Supported in part by a grant from the Health Future Foundation to the Creighton University Gastrointestinal Diagnostic and Research Center.

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Methods

Esophageal Manometry

Esophageal manometry was performed according to the technique described by Winans and Harris,[6] using a single-catheter assembly consisting of 3–5 fluid-filled polyethylene tubes bonded together with 3–5 lateral openings placed at 5.0-cm intervals from the distal end of the catheter and radially oriented 72–120 degrees apart. The diameter of the lateral openings was 2.0 mm in the three-lumen catheter and 0.8 mm in the five-lumen catheter. A constant infusion of distilled water was delivered initially by a Harvard infusion pump (Harvard Apparatus, South Natick, MA) through the three-lumen catheter, and subsequently, by an Arndorfer pneumohydraulic low compliance system (Arndorfer Medical Specialties, Inc., Greendale, WI) through the five-lumen catheter. The rate of infusion was 3.6 mL/min with the former and 0.6 mL/min with the latter. Studies obtained with the two infusion techniques were compared in a group of 14 subjects, and a correction factor was calculated to give uniformity of measurements between the two systems.

The catheter was passed into the stomach and withdrawn in 1.0-cm increments back into the esophagus, and from the esophagus into the pharynx. The overall length, the abdominal length, that is, the length below the respiratory inversion point, and the mean resting pressure of the distal esophageal sphincter were measured. Patients with a sphincter pressure of 6.0 mmHg or less, an overall sphincter length of 2.0 cm or less, and/or a length of sphincter exposed to intra-abdominal pressure of 1.0 cm or less were considered to have a mechanically defective cardia.[7] Distal esophageal sphincter relaxation was evaluated with five dry and five wet swallows, and was considered normal when the sphincter pressure dropped to the gastric baseline. The mean amplitude of the contractions, and the incidence of repetitive and simultaneous contractions in the distal esophageal body were noted during ten dry and ten wet swallows. Patients with a mean contraction amplitude of less than 20 mmHg and/or an incidence of repetitive or simultaneous waves greater than 30% were considered to have a nonspecific motility disorder of the esophageal body.[8] The length and mean resting pressure of the upper esophageal sphincter and the peak pharyngeal pressure were similarly measured.

Twenty-four hour Esophageal pH Monitoring

Twenty-four hour esophageal pH monitoring was performed according to a technique previously described,[1] with a pH electrode placed 5.0 cm above the upper border of the distal esophageal sphincter as measured by manometry. Acid reflux was defined whenever the pH in the esophagus dropped to 4 or less. Esophageal acid exposure was assessed by a composite mathematical score using EsopHogram software (Gastrosoft Inc., Milwaukee, WI) that incorporated six components of the 24-hour record: (1) percentage of time the esophageal pH was 4 or less for the total 24-hour period, (2) for the time in the upright position, (3) for the time in the supine position, (4) the total number of reflux episodes, (5) the number of episodes lasting 5 minutes or longer, and (6) the duration of the longest episode. Individuals whose cumulative score exceeded by more than two standard deviations the mean score of control subjects were considered to have an abnormal esophageal acid exposure.[9]

Investigation into the Cause of the Stricture

Based on the analysis of clinical history, endoscopic findings, and esophageal function studies, the patients were categorized as to the most valid cause for their stricture. Patients who had increased esophageal exposure to acid gastric juice on 24-hour pH monitoring were considered to have a reflux etiology. Patients who had a normal 24-hour pH study, or who were unable to have esophageal function studies performed, were intensely investigated for further clues regarding the cause of their stricture, including a complete history of drug consumption before the onset of the dysphagia.

Results

Twenty-four-hour esophageal pH monitoring showed an abnormal esophageal acid exposure in 41 (79%) of the 52 patients studied. These patients were considered to have a reflux etiology for their stricture.

Eleven patients had a normal 24-hour pH study and three patients could not be studied because of the inability to dilate the stricture in two patients and the presence of a Zenker's diverticulum in one patient. Table 1 shows the pertinent clinical information obtained from these 14 patients by focused questioning, endoscopy, and, when possible, esophageal manometry. The evidence suggested that the cause of the stricture was drug injury in 11 patients, alkaline reflux after gastrectomy in two patients, and gastroesophageal reflux in one patient. Thus, 11 of the initial 55 patients had strong evidence for a drug-induced stricture. This represents a prevalence of 20% in the overall referred population.

Seven of the 11 patients with a drug injury had underlying esophageal pathologic conditions. Four patients had an esophageal motility disorder, three patients had a greater than 30% incidence of repetitive and simultaneous contraction on swallowing, and one patient showed aperistalsis of the esophageal body with incomplete distal esophageal sphincter relaxation. Three other

TABLE 1. *Pertinent Clinical History and Findings in Patients with Normal Esophageal Acid Exposure or Unable to be Monitored (N = 14)*

Patient/Sex	Age	Duration Dysphagia	History	Stricture Location (cm incisors)	DES P (mmHg)	DES OL (cm)	DES AL (cm)	Amplitude Esophageal Contractions (mmHg)	Biopsy	Surgical Pathology
1/F*	77	21 yrs	Drug ingestion, Heller myotomy	27	11.2	4.2	1.2	0	Fibrosis	Chronic inflammation, ulceration, fibrosis
2/M*	61	2 mos	Drug ingestion after coronary artery bypass	38	15.0	3.4	3.0	150 (>30% REP)	Fibrosis, fibropurulent exudate	—
3/M*	45	6 mos	Drug ingestion	38	17.0	3.2	2.6	30	Chronic inflammation, fibrosis, dysplasia	—
4/M*	25	6 yrs	Drug ingestion, Schatzki ring	40	22.0	2.8	2.0	25	Acute and chronic inflammation	—
5/M*	26	1 yr	Drug ingestion	40	10.0	2.8	1.4	40 (>30% SIM)	—	—
6/F*	76	8 yrs	Drug ingestion, reflux symptoms, hiatal hernia	22	—	—	—	—	Acute inflammation with ulceration	Submucosal fibrosis
7/F*	58	2 mos	Drug ingestion	27	—	—	—	—	—	Ulceration with acute and chronic inflammation, full-thickness fibrosis
8/M*	54	11 yrs	Drug ingestion	22	22.3	4.0	2.7	80	Inflammation and dysplasia at 22–35, squamous epithelium below	Acute and chronic inflammation, squamous metaplasia esophageal glands, mucosal fibrosis
9/M*	36	2 yrs	Drug ingestion	19	13.8	3.5	2.1	60	Chronic inflammation, mild hypercheratosis	Fibrosis with chronic inflammatory cells and granulation tissue
10/M*	34	14 yrs	Drug ingestion, Schatzki ring	38	5.6	2.8	1.0	40	Focal ulcer, acute and chronic inflammation	—
11/F*	69	3 yrs	Drug ingestion	18	3.0	2.8	0.2	130 (>30% REP)	Focal ulcer, acute and chronic inflammation	—
12/M	51	3 yrs	Billroth II	37	10.0	2.7	1.3	40 (>30% SIM)	Achantosis	Acute and chronic inflammation, ulceration, fibrosis
13/M	52	1 yr	Gastrectomy, Roux-Y esophagojejunostomy	36	2.0	3.0	1.0	50	Acute and chronic inflammation	—
14/M	86	6 mos	Reflux symptoms, hiatal hernia, Zenker's diverticulum	25	—	—	—	—	Barrett's esophagus	—

* Considered to have a drug-induced stricture.
DES = distal esophageal sphincter.
P = pressure.
OL = overall length.
AL = abdominal length.
SIM = simultaneous contractions.
REP = repetitive contractions.

TABLE 2. *Cause and Treatment of Drug-induced Esophageal Strictures*

Patient	Medication	Period of Exposure	Therapy	Result
1	Potassium chloride	3 mos	Dilatation with progressive difficulty, resection and colon interposition	Good (8 yrs)
2	Potassium chloride	2 weeks	Dilatation (N = 45)	Good (3 yrs)
3	Doxycycline hyclate	1 yr	Dilatation (N = 1)	Good (10 mos)
4	Acetylsalicylic acid	1 week	Dilatation (N = 1)	Good (20 mos)
5	Tetracycline hydrochloride	6 mos	Dilatation (N = 4)	Good (2 yrs)
6	Potassium chloride	1 yr	Unable to dilate, colon bypass	Good (6 yrs)
7	Ascorbic acid	2 mos	Perforation during dilatation, resection and colon interposition	Good (18 mos)
8	Phenytoin sodium	6 yrs	Dilatation with progressive difficulty, sleeve resection	Induced gastroesophageal reflux (5 yrs)
9	Doxycycline hyclate	1 yr	Dilatation with progressive difficulty, excision fibrous ring and esophageal myotomy, colon bypass	Good (2 yrs)
10	Acetylsalicylic acid	1 week	Dilatation (N = 1)	Good (9 mos)
11	Quinidine	4 mos	Dilatation (N = 1)	Good (3 mos)

patients had roentgenographic esophageal abnormalities that could potentially interfere with transit of a drug through the esophagus: these were two patients with a Schatzki's ring and one patient with a hiatal hernia and gastroesophageal reflux.

Table 2 summarizes the drug history and therapy of the 11 patients considered to have a drug etiology of their stricture. All of the patients were initially treated with dilatation. This was successful in six patients, with the number of dilatations ranging from 1–45. Dilatation was of temporary benefit in three patients and unsuccessful in two. In one of these five patients the dilatation resulted in a perforation and required resection of the esophagus and colon interposition. In another patient esophageal resection and colon interposition was required to establish oral alimentation (Fig. 1). In the third patient, because of operative risk factors, a substernal colon bypass of the strictured esophagus was performed (Fig. 2). In the fourth patient, because of the localized disease, a sleeve resection of the esophagus was performed (Fig. 3). The fifth patient had excision of a fibrous ring and an esophageal myotomy, but required a substernal colon bypass to the pharynx when the stricture reoccurred. (Fig. 4). The specimen in the two patients who had esophagectomy showed mucosal ulceration and panmural fibrosis at the stricture site (Fig. 5). Results of surgery were satisfactory in all patients except for the patient who had the sleeve resection. In this patient, the procedure resulted in pulling the esophagus up into the thorax causing a reduction of distal esophageal sphincter pressure, a decrease of abdominal sphincter length, and the induction of gastroesophageal reflux confirmed by 24-hour pH monitoring (Table 3).

Prospective Clinical Study

Studied Population

Eighteen individuals volunteered for a prospective study designed to evaluate the probability for a medicinal capsule to lodge in the esophagus. The volunteers were free of clinical disease as judged by history and physical examination. There were 11 men and seven women. The population was divided into two age groups. Nine volunteers were under 70 years of age (mean age: 32 years, range: 21–49 years), and nine were over 70 years (mean age: 76-years, range: 71–81 years). The reason for dividing the population at this age was the decline in the amplitude of esophageal contractions observed in individuals over the age of 70.[10] In each volunteer, the esophageal transit time of a gelatin capsule containing radioactive material was measured when ingested with a small- and large-volume water bolus. Twelve of the 18 volunteers consented to esophageal manometry.

Normal values for esophageal motility were obtained from a group of 20 control subjects, 10 men and 10 women, with a mean age of 38 years, ranging from 20–71 years. All control subjects were free of esophageal disease as assessed by history, barium roentgenographic study, and 24-hour esophageal pH monitoring.

Methods

Esophageal Transit Scintigraphy

A radionuclide marker was placed over the cricothyroid notch of each volunteer or control subject to denote the position of the cricopharyngeus, *i.e.*, the esophageal inlet. A 25-mL bolus of water labeled with a 250-μCi dose of Tc-99M sulfur colloid solution was administered orally to define the esophageal anatomy.[11] Images were obtained every 0.3 second for 60 seconds with the subject initiating dry swallows at 15-second intervals. Computerized composite imaging was used to develop an anatomic picture of the esophagus, esophagogastric junction, and stomach. This allowed for accurate placement of computer-generated regions of interest.

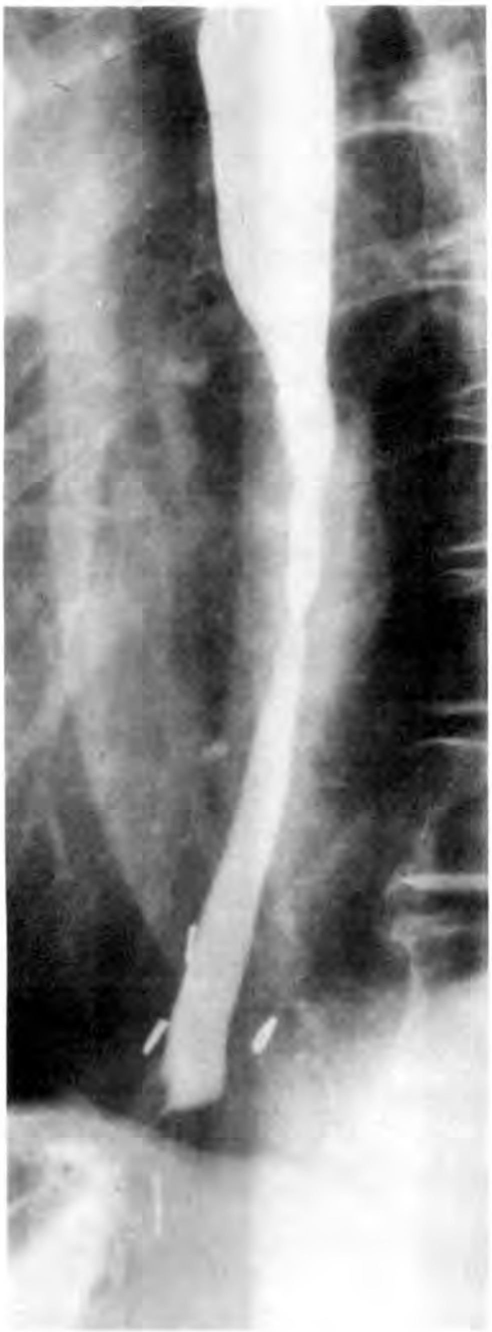

FIG. 1. Barium esophagogram in patient 1 with achalasia showing midesophageal stricture secondary to ingestion of potassium chloride. The degree of tissue injury is reflected by the thickness of the companion shadow. The hemostatic clips are from a previous Heller myotomy. The stricture was unable to be dilated and an esophageal resection with colon interposition was performed. Histologic examination of the surgical specimen showed squamous epithelium above and below the strictured segment.

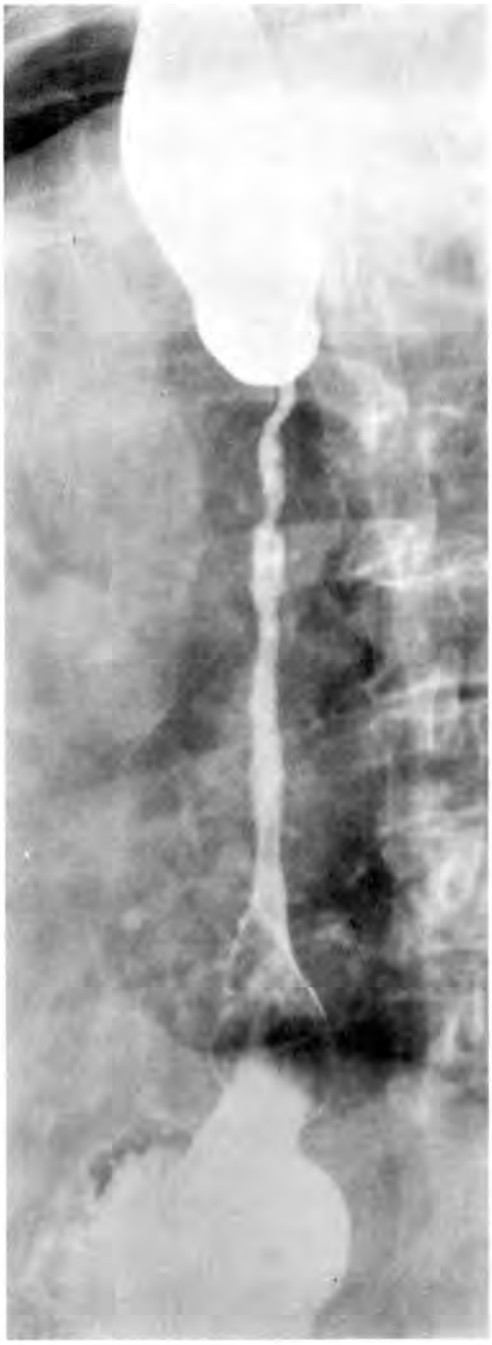

FIG. 2. Barium esophagogram in patient 6, showing a long esophageal stricture secondary to gastroesophageal reflux and the ingestion of potassium chloride. Note the presence of a hiatal hernia. The stricture was unable to be dilated, and because of the patient's age and physiologic status, a substernal colon bypass was performed.

A radiolabeled gelatin capsule was prepared by adding

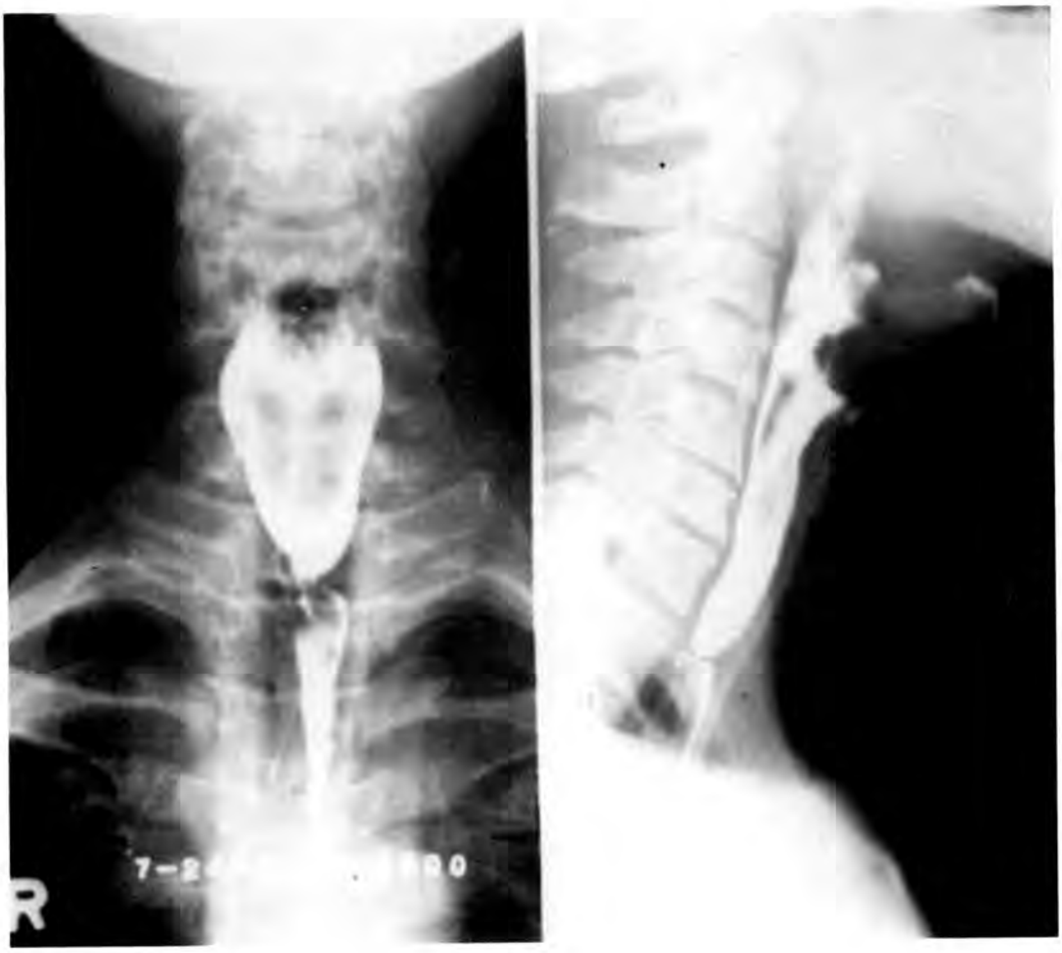

FIG. 3. Barium esophagogram in patient 8, showing a short esophageal stricture in the upper esophagus secondary to ingestion of phenytoin. Dilatation did not relieve dysphagia and the stricture was excised by a sleeve resection of the esophagus. This resulted in gastroesophageal reflux.

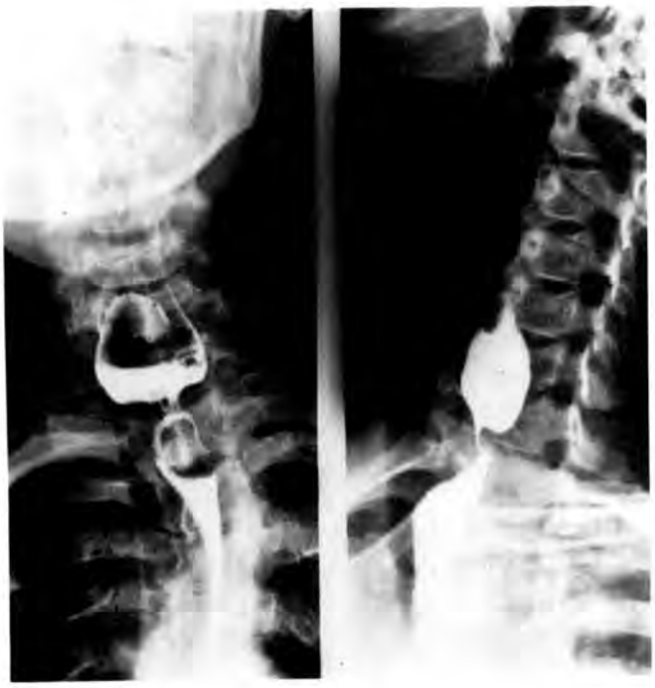

FIG. 4. Barium esophagogram in patient 9, showing a high esophageal stricture secondary to ingestion of doxycycline. Excision of a fibrous ring and an esophageal myotomy were initially performed. Dysphagia recurred in 4 years, requiring a substernal colon bypass to the pharynx.

a 250-μCi dose of Tc-99M sulfur colloid solution to the inside lumen of an empty soft #2 gelatin capsule. This capsule was then progressively nested inside a #1, #0, and #00 empty soft gelatin capsule. The final product was a #00 radiolabeled gelatin capsule weighing 1.06 g with a barrier of four layers of gelatin between the internal liquid contents and the outer capsule environment. This technique was used to prolong capsule dissolution and subsequent release of the radiolabeled internal liquid contents for up to 10 minutes. It also provided additional weight to the capsule to simulate more closely the density of most commercially available medicinal capsules.

The volunteers were instructed to swallow the radiolabeled gelatin capsule with a 120-mL water bolus while in the upright position. Images were obtained every 0.3

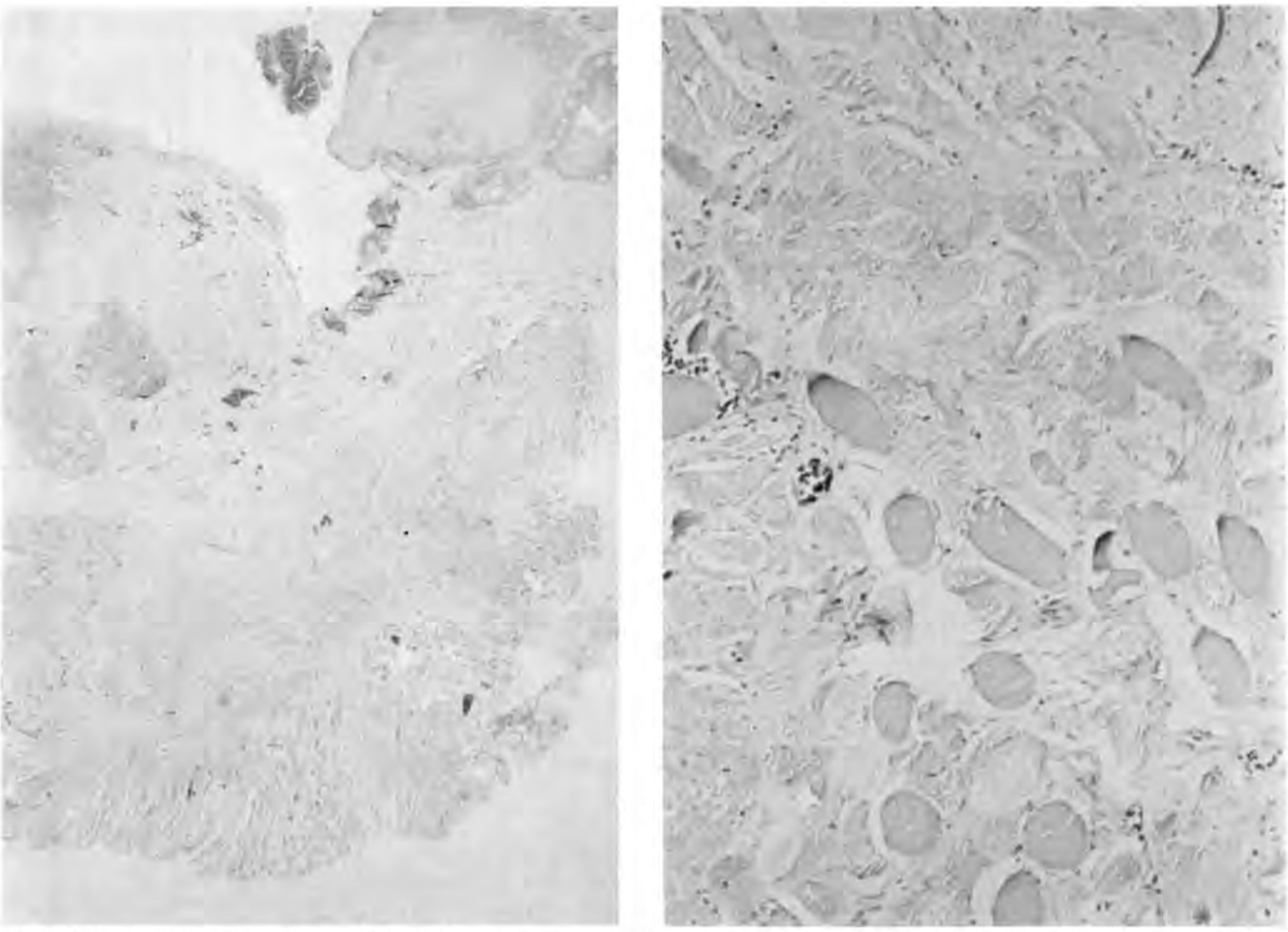

FIG. 5. *Left.* microphotograph of the surgical specimen of patient 8, showing an esophageal ulcer with transmural fibrosis (hematoxylin and eosin, original magnification ×10). *Right.* higher magnification (original magnification ×250) of esophageal muscle fibers with intramural fibrosis. The degree of tissue damage explains the failure of dilatation to relieve dysphagia.

second for 60 seconds with the individuals swallowing at a 15-second interval. Additional images were obtained at 2-minute intervals for up to 10 minutes when the capsule lodged in the esophagus to document the eventual passage of the capsule or its dissolution with the release of the radionuclide solution into the esophagus. The same procedure was then repeated in all volunteers using an identically prepared radiolabeled gelatin capsule administered with only a 15-mL water bolus.

Esophageal Manometry

The methods are the same as described for the retrospective clinical study.

TABLE 3. *Function Studies Before and After Sleeve Esophageal Resection*

	Distal Esophageal Sphincter			Amplitude Esophageal Contractions (mmHg)	24-hour pH Test Score
	P (mmHg)	OL (cm)	AL (cm)		
Preoperative	22.3 ± 3.2	4.0 ± 1.0	2.7 ± 0.5	80 ± 17	Normal
Postoperative	13.3 ± 3.2	4.5 ± 0.6	1.0 ± 0.0	65 ± 18	Abnormal
P*	<0.05	NS	< 0.01	NS	

* p calculations are based on comparison of the mean ± SD of three preoperative and three postoperative manometric measurements.

P = pressure.

AL = abdominal Length.

OL = overall Length.

NS = not significant.

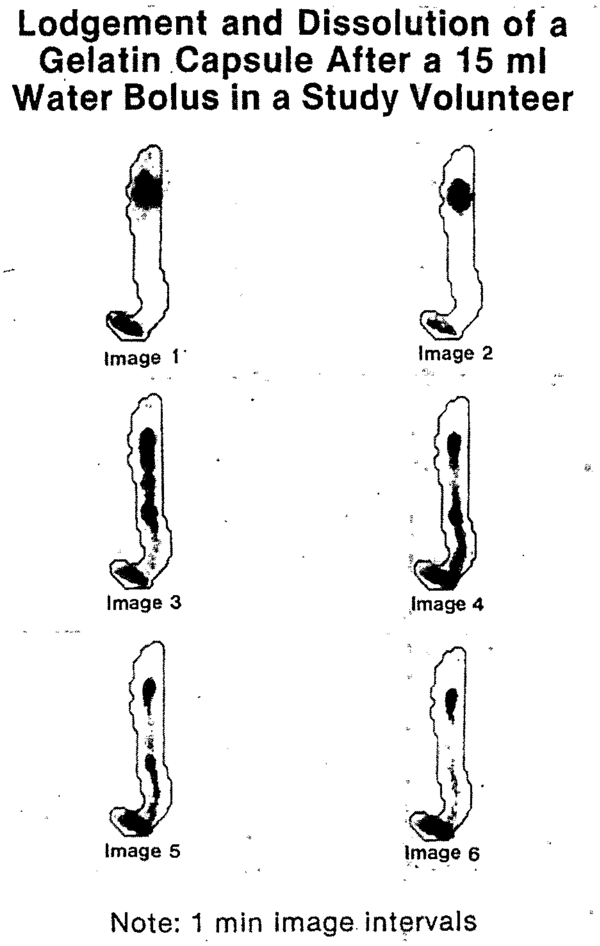
Lodgement and Dissolution of a Gelatin Capsule After a 15 ml Water Bolus in a Study Volunteer
Image 1
Image 2
Image 3
Image 4
Image 5
Image 6
Note: 1 min image intervals

FIG. 6. Lodgment of the gelatin capsule in the esophagus with dissolution of the gelatin and release of the radionuclide into the esophageal lumen. Capsule was ingested with a 15-mL bolus of water.

Results

Esophageal Transit Scintigraphy

The capsule given with the 15-mL water bolus lodged in 11 of the 18 volunteers (61%), at the level of the aortic arch in seven (Fig. 6) and at the gastroesophageal junction in four. Figure 7 shows that the capsule lodgment occurred at sites similar to the location of the drug-induced esophageal strictures in the 11 patients reported in Table 2. The capsule lodged in five of the nine volunteers under the age of 70, and in six of the nine volunteers age 70 or greater.

When the 120-mL water chaser was used, lodgment occurred in three (17%) of the 18 volunteers, at the level of the aortic arch in one and at the gastroesophageal junction in two. All three of these volunteers were over 70 years of age. The capsule did not lodge in any of the volunteers under the age of 70 when taken with 120 mL of water.

Overall, the capsule lodged in 11 of 18 volunteers. In three of the 11, lodgment occurred even when the volume of water chaser was increased to 120 mL. The incidence of capsule lodgment with the 15-mL bolus statistically differed from the incidence of capsule lodgment with the 120-mL bolus (61% *vs.* 17%, $p < 0.005$). Thus, increasing the volume of water chaser caused a decrease in the incidence of capsule lodgment by 44%.

Esophageal Manometry

In the 12 volunteers examined, the mean distal esophageal sphincter pressure, the degree of sphincter relaxation, and the mean amplitude of esophageal contractions on dry and wet swallows did not statistically differ from the reference values obtained from the control subjects. Three of the 12 volunteers had a nonspecific esophageal motility disorder, *i.e.,* a greater than 30% incidence of repetitive or simultaneous contractions. All three were over 70 years of age. In one of the three, the capsule lodged with the 120-mL water chaser. Volunteers in whom the capsule lodged with the 120-mL bolus showed a lower mean amplitude of esophageal contractions with wet swallows, compared with those in whom the capsule lodged with only the 15-mL bolus ($p = 0.05$), suggesting they had less propulsive force in the body of their esophagus.

In Vitro Experimental Study

Methods

An *in vitro* evaluation of dissolution time was performed on the drugs responsible for the esophageal le-

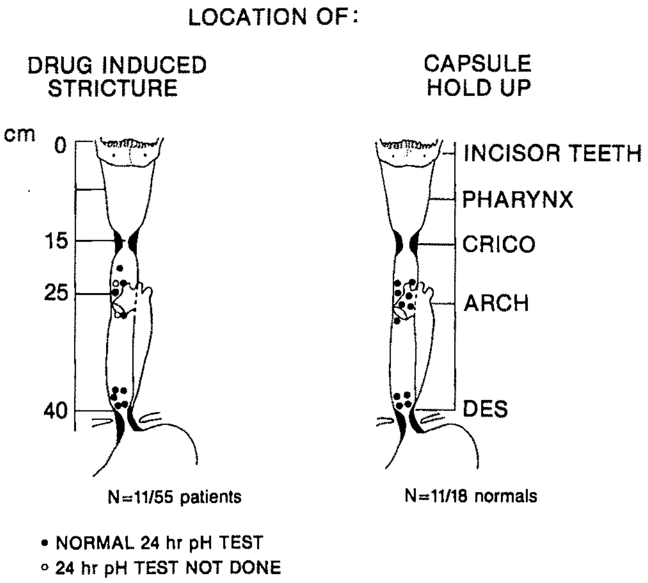

FIG. 7. Schematic drawing of the esophagus showing that the site of capsule lodgment in 11 volunteers after a 15-mL water chaser was similar to the location of drug-induced stricture in the 11 patients reported in Table 2.

TABLE 4. *Dissolution Time and pH of Drugs Observed to Cause Esophageal Injury*

	pH Saliva	Start Dissolution Time (Min)	Complete Dissolution Time (Min)	pH at Complete Dissolution
Potassium chloride, 750 mg (slow-release tablet)	6.3	—	>720	6.5
Potassium chloride, 750 mg (elixir)	6.4	—	—	6.6
Doxycycline hyclate, 100 mg (capsule)	6.1	7.0	37	3.2
Tetracycline hydrochloride, 250 mg (capsule)	6.2	10.0	42	1.6
Acetylsalicylic acid, 325 mg (tablet)	6.3	1.5	5	3.4
Ascorbic acid, 500 mg (tablet)	6.2	1.0	58	2.8
Phenytoin sodium, 100 mg (capsule)	6.1	8.0	15	10.4
Quinidine gluconate, 324 mg (sustained-release tablet)	6.4	—	>720	6.9

sion in the 11 patients. A standard dose of medication was placed in a test tube containing 10 mL of saliva. The time was noted when dissolution of the capsules or tablets started and when completed. The pH of the saliva was recorded throughout the course of the experiment using a Beckman pH electrode (Beckman Instruments, Inc., St. Louis, MO) connected *via* a pH meter to a strip chart recorder running at a speed of 2.5 cm/min.

Results

Table 4 shows that, with the exception of potassium chloride and quinidine, the slow-release tablets, dissolution of all preparation started within 10 minutes, was completed by 60 minutes, and was associated with a marked shift in pH. No pH change was observed with potassium chloride and quinidine, suggesting that local concentration of a drug is the important factor in producing mucosal damage.

Discussion

We were surprised that 11 (20%) of the 55 patients referred for therapy of a benign esophageal stricture had a drug-induced etiology. In six of the 11 patients, this was suggested by the location of the stricture and/or a normal 24-hour pH test. In five patients, the drug-induced stricture was located in the distal esophagus and would have been assumed to be due to gastroesophageal reflux if the 24-hour pH study had not been normal. This suggests that the true incidence of drug-induced esophageal strictures in patients referred for surgery is probably underestimated, since it is common practice to assume gastroesophageal reflux as the cause when the stricture is located in the distal esophagus.[12]

A drug etiology for an esophageal stricture should be considered when, after dilatation, the patient has a normal esophageal acid exposure on 24-hour pH monitoring and a history of drug ingestion. When there is no history of drug ingestion, other causes for the stricture must be investigated. The most common is alkaline gastroesophageal reflux in a patient with achlorhydria[13] or previous gastric surgery.[14]

Over the past 15 years, clinical and experimental reports have shown that lodgment of ingested pills in the esophagus can occur,[15,16] and that a variety of medications can produce esophageal injury[3,4] (Table 5). Initially, a drug-induced esophageal injury was believed to be limited to subjects with underlying esophageal pathologic conditions. Subsequently, it became evident that most patients with the problem were apparently free of esophageal abnormalities.[3] This focused investigation on factors that influenced the transit of tablets or capsules through the esophagus, such as the position of the body on swallowing, the density, size, and shape of the capsules or tablets, and the volume of the fluid chaser.[16] Medications known to be corrosive, such as potassium chloride, have been prepared in a powder form or slow-release tablets to avoid a high localized concentration. Despite these efforts, drug-induced esophageal injury still remains a complication of medicinal therapy. The *in vitro* study reported showed that most medications with a potential for causing esophageal injury, when mixed with saliva, have a dissolution time within 60 minutes. This property, plus the holdup of tablets or capsules in the esophagus, can result in tissue injury

TABLE 5. *Drugs Reported to Cause Esophageal Injury*

	No. of Cases
Doxycycline hyclate*	98
Emepronium bromide	36
Potassium chloride*	19
Ferrous sulfate or succinate	12
Tetracycline hydrochloride*	12
Alprenolol chloride	9
Quinidine sulfate or gluconate*	8
Acetylsalicylic acid*	6
Clindamycin hydrochloride	4
Indomethacin	3
Ascorbic acid*	2
Phenytoin sodium*	1

* Drugs reported in the current study.
Modified and updated from reference #3.

from a high localized drug concentration at an excessive pH. Prevention will require the design of a capsule or tablet to reduce their tendency to lodge in the esophagus, and better chemical formulation of the medication to prevent high local concentrations. This may be achieved by the development of large chewable pills with less drug concentration and a more neutral pH.

In our prospective study the main predisposing factors for lodgment of a capsule in the esophagus were the volume of the water chaser and the age of the subject. Individuals over 70 years of age had a decrease in the amplitude of esophageal contractions. Even when a full glass of water was given with the medication, one third of these individuals had the capsule lodge in the esophagus. Consequently, educating patients to take medications with a full glass of water will reduce the incidence of lodgment but is unlikely to eliminate the problem.

As one would expect, patients with underlying esophageal abnormalities are prime candidates for a drug-induced esophageal injury, and a special effort in preventive education should be extended to them. The presence of an esophageal abnormality, such as a motility disorder, hiatal hernia, Schatzki's ring, or reflux-induced esophagitis and stricture, can increase the probability of capsule or tablet lodgment. The former two are associated with an increased transit time[17,18] and the latter two are known causes for holdup of solids in the distal esophagus.[19,20] We suspected in one of our patients that the combination of reflux esophagitis and entrapment of a medicinal tablet contributed to the development of a severe stricture that could not be forcibly dilated. Most reflux-induced strictures can be dilated since the fibrosis is limited to the submucosa. When there is transmural fibrosis, as in lye strictures, dilatation often cannot be accomplished, or if so, is often ineffective in relieving the symptoms of dysphagia. When a stricture that appears to be due to reflux cannot be dilated or the results of dilatation are unsatisfactory, the possibility of a superimposed drug injury should be investigated.

Open heart surgery may also predispose to drug-induced esophageal injury.[2] We believe that esophageal clearance was adversely affected in one of our patients by hypothermia of the esophageal muscle during coronary artery bypass, and compression of the distal esophagus by the heart after its pericardial support has been lost by the pericardiotomy. In this situation, potassium chloride, even in the liquid form, may not be cleared from the esophagus especially in the supine position.

Patients with a drug-induced esophageal stricture do not require an antireflux repair. In most situations, dilatation of the stricture is sufficient to relieve dysphagia. In a review of drug-induced esophageal injury, Oakes and Sherck reported 17 strictures, all of which responded to dilatation.[21] This therapy was successful in six of our 11 patients, even though one patient required 45 dilatations over a 2-year period. In the other five patients, an attempt to dilate the stricture was unsuccessful and in one patient resulted in perforation of the esophagus. The inability to dilate the stricture is an indication for esophageal resection with colon interposition. The resected surgical specimens from these patients showed dense full-thickness fibrosis, and reflect the severity of the esophageal injury that can be caused by drugs. In older patients with high surgical risk, or in patients with extensive fibrosis at the stricture site, a substernal colon bypass can be performed. A limited esophageal sleeve resection may represent a tempting solution for localized short strictures, but the potential for causing gastroesophageal reflux, secondary to increased longitudinal tension and loss of intra-abdominal esophagus, should discourage its use. This was well documented in one of our patients and has convinced us of the inadvisability of this approach.

During the course of this study, it has occurred to the authors that the well-known but poorly understood esophageal web of the Plummer–Vinson syndrome may actually be a drug-induced lesion. Since these patients have an iron deficient anemia, it would be logical for physicians to prescribe ferrous sulfate, a drug known to cause esophageal injury (Table 5). It is reasonable to suspect that a number of such patients may have had a drug-induced esophageal injury develop at the site where the web is commonly observed. Not knowing the cause of the esophageal abnormality, the early observers reported the web as part of the syndrome.[22]

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Esophagectomy Without Thoracotomy: Is There a Risk of Intramediastinal Bleeding?

A Study on Blood Supply of the Esophagus

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In transhiatal blunt esophagectomy there is surprisingly little bleeding if no adjacent great vessels are torn. This prompted an investigation by new injection techniques and corrosion on the human esophageal vasculature three-dimensionally. The three main arterial sources were confirmed: the superior thyroid artery, bronchial arteries at the level of the carina, and the left gastric and splenic artery. Two facts became obvious that were not appreciated hitherto. All major vascular trees divide into minute branches at some distance from the esophagus. Those branches go on to form a dense submucosal interconnected network. It appears that such small extraesophageal branches, when torn, will have the benefit of contractile hemostasis. Previous claims made that essential nutritional vessels arise from intercostal phrenic arteries or the aorta directly could not be confirmed. These findings would confirm blunt esophagectomy for tumors within the wall of the organ as a relatively safe procedure in terms of bleeding hazards.

THE BLUNT PULL through esophagectomy without thoracotomy for esophageal lesions with cervical esophagogastric anastomosis initially proposed by Denk[1] and successfully done in humans by Grey-Turner[2] has fallen in almost complete oblivion but recently found an increasing number of advocates.[3–7] It is described as a relatively safe approach with moderate blood loss[8–15] (see also Table 1). It appears to greatly reduce the danger of septic mediastinitis caused by anastomotic leakage. The three decades of oblivion have most likely been caused by two facts: the advent of safe thoracotomies has placed emphasis on direct approach to the organ with intrathoracic esophagogastro or esophagojejuno anastomoses. Although this currently appears to be a procedure with acceptable mortality rates, it remains that any anastomotic leakage in the thorax is a life-threatening complication.[8,16–18] The second reason for discontinuing the use of blunt esophageal dissection were schemes of vascular supply of the esophagus in textbooks of anatomy and surgery that suggested major arteries supplying the esophagus from the intercostal vessels and directly from the aorta. In view of those schemes it seemed extremely hazardous to engage in any blunt dissection of such a well-vascularized organ.

The relatively few investigators of human esophageal vascularization referred to classical macroscopic assessment at autopsy and therefore only reported on the larger stem vessels.[19–21] Intramural anastomoses shown by fluoroscopy after *in situ* barium injection[19,22] did not outline well the arterial pattern because of the overlying arteries of adjacent structures.[23] This also holds true for angiography *in vivo*.[24] The technique of corrosion casts,[25] which produces realistic, three-dimensional replicas of the vascular system of small solid organs, was not used for large hollow organs such as the esophagus and stomach. This technique, when properly modified, was hoped to clearly display both the large extraparietal arterial sources as well as the details of the microvascular connections and provide the answer to the following three questions: (1) Can the classical vascular sources of arterial blood supply to the esophagus: cervical, thoracic and abdominal, be confirmed? (2) What is the microvascular pattern of arterial blood supply to the esophagus and how much interconnection exists between the arterial territories of the esophagus? (3) How is it that in the face of a fairly large size of mediastinal arterial source (the bronchial artery) blunt dissection can be done without deleterious hemorrhage?

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TABLE 1. *Complications due to Blunt Esophagectomy*

Year	Senior Author	No. of Cases	Mediastinal Hemorrhage	Mean Blood Loss (mL)	Tracheal Tear	Pneumothorax	Recurrent Nerve Probe	Anastomotic Leak§
1971	Akiyama[3]	1	—	—	—	—	—	—
1974	Kirk[33]	5	0	—	0	2	1	0
1977	Thomas[14]	4	1	Minimal	0	0	0	0
1978	Orringer[5]	26	0	—	0	8	5	4
1979	Szentpetery[13]	17	(10)*	Minimal	1	0	1	0
	Bains[31]	16	0	—	10‡	16	0	0
	Cordiano[32]	14	0	—	0	1	0	1
1980	Akiyama[4]	41	0	—	0	0	1	4
1981	Pinotti[7]	25	0	—	0	5	5‡	0
	Steiger[18]	21	0	—	0	4	2‡	4
1982	Tryzelaar[38]	13	0	Minimal	0	2	0	1
1983	Orringer[6]	143‖	2	900	2	73	47‡ (-3)	6
1984	Neff[29]	14	1 AV†	800	0	0	0	0
1985	Finley[9]	34	1 AV	900	0	0	(12)‡	7
	Ulrich[15]	105	2 AV†	1100	2	62	5	31
1971–1985		453	7 (1.6%)	~900	15 (3%)	173 (38%)	79 (17%)	58 (13%)

* Insignificant mediastinal hemorrhage was reported in three cases and hemothorax in 10 cases.

† Fatal bleeding from the azygos vein (AV) was a fatal complication and led to 0.7% intraoperative mortality rate.

‡ Problems concerning the recurrent laryngeal nerve were reported as being transient and only three times (−3) required reoperation.

§ Most anastomotic leaks closed spontaneously.

‖ Orringer's report of 1983 contains the patients of his report of 1978.

Materials and Methods

Eighteen human specimens were subjects of this study; 11 were male and seven were female, aged 36–80 years. All subjects with a previous abdominal history, vascular disease, or diabetes were excluded. Sixteen of the specimens were injected with the resin Beracryl (Acryl-Industrie-Kunststoff, Troller AG, CH 4854 Fulenbach, Switzerland) and two specimens were injected with Mercox-(Vilene Co., Ltd., Tokyo, Japan).

Preparation

At autopsy, 9–24 hours postmortem, a large specimen containing the upper intestinal and chest organs, the tongue, a 15-cm cuff of diaphragmatic muscle, and the entire aorta was removed *en bloc.* We took great care not to avulse the intercostal arteries from the aortic origin, preserving stumps of at least 2–4 cm in length. The heart was dissected close to the aortic valve; lungs, liver, spleen and kidneys were removed at the organ hilum. We secured a Foley catheter (Rüsch® 22-26 Charriere, Switzerland) in the caudal aorta (Fig. 1) and irrigated the vessels with deaerated water to which Heparin (Liquemine®) was added to remove clots. Torn or divided collaterals from adjacent organs were detected by leakage of fluid and ligated. Ligature of the cranial aorta established a closed circuit.

To stabilize the intestinal cavities and to avoid collapse of the esophagus and stomach during the subsequent procedures, we placed an intestinal tube into the esophagus and a balloon (condom) into the stomach. This balloon was filled with water.

Injection

We used two resins of different viscosity: (1) For the macroscopic display of the arteries, the synthetic cold-

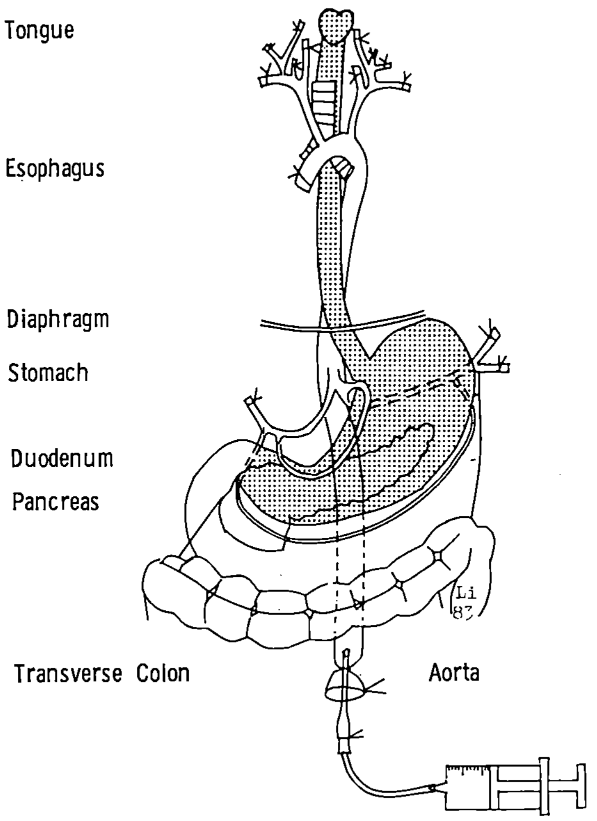


FIG. 1. *En bloc* specimen ready for Beracryl injection with Foley catheter in the aorta. All arteries supplying organs other than shown were ligated.

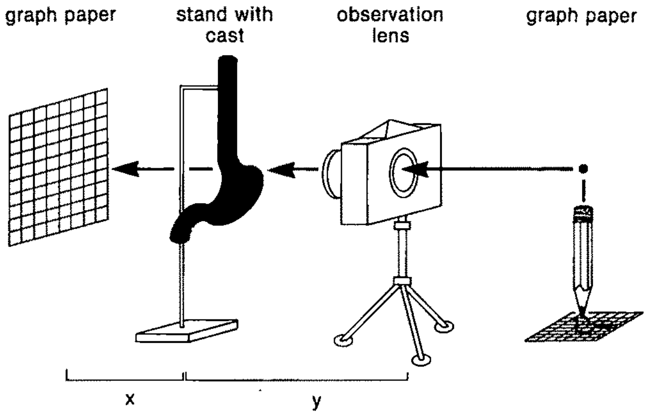


FIG. 2. Method of reproduction of the arterial tree. The cast was placed in front of the graph paper and its dimensions transferred on a second graph paper as viewed through a lens. The distances between cast and graph paper (x) and lens (y) were constant in all the reproductions.

setting Beracryl was used. This fluid polymer/solid monomer catalyst had powder particles of 160 μm, thus allowing flow into arteries of 0.2–0.1 mm internal diameter. Through the Foley catheter we injected by hand 400–500 mL of the liquid until a clear resistance occurring after 5 minutes indicated the completeness of the injection. (2) For the display of the microcirculation, the synthetic cold-setting Mercox was used. This product had a viscosity that allowed flow through the arteries and through the capillaries into the veins. However, its use is limited to specimens of small size.[26] Therefore, the left gastric artery was injected; 150 mL of the resin were needed.

Care was taken not to stir air into the resins while mixing the components; we did not use machines for injection[25,27] because this caused burst of vessels in our previous studies.[23,28,29]

During the injection and the subsequent procedures, the specimens were submerged in a large container (55 × 40 × 25 cm), filled with 10–15 L of lukewarm water; any change in position was avoided. After 20 minutes we added formaldehyde to make a 5% solution, in which the casts remained until they were fully hardened 12–20 hours later. Shrinkage of the entire specimen was 1–3%.

Corrosion

We changed the formaldehyde solution for 30% caustic soda and placed the container in a water tank (Mazerationsanlage, Fa. Handschin, CH 4000 Basel, Switzerland). Being at a constant fluid temperature between 50 and 60 C, the organic tissues of the specimens were macerated after 15–30 hours. The vascular cast was rinsed in water, carefully cleaned, and mounted on a stand to air dry. To ensure that the casts had not been damaged, we routinely filtered the content of the containers for residuals.

Documentation

The casts on their stand were photographed and sketches were also made. To this effect, they were placed at a distance of 30 cm in front of a large sheet of graph paper and carefully recorded as illustrated in Figure 2.

The various diameters of the vessels were measured using a binocular magnifier. These were compared with gastric, pancreatic, and middle colic vessels. The values obtained from the casts refer to the internal diameter of an artery and, therefore, the arteries seem to be of smaller size than those observed during surgery.

The clean Mercox casts were cut in suitable small blocks and mounted on stubs with glue. The blocks then were gold sputtered and inspected in a stereoscan. SEM photographs were taken of the various aspects (Dr. Düggelin, REM Labor, Universität Basel, Switzerland).

Results

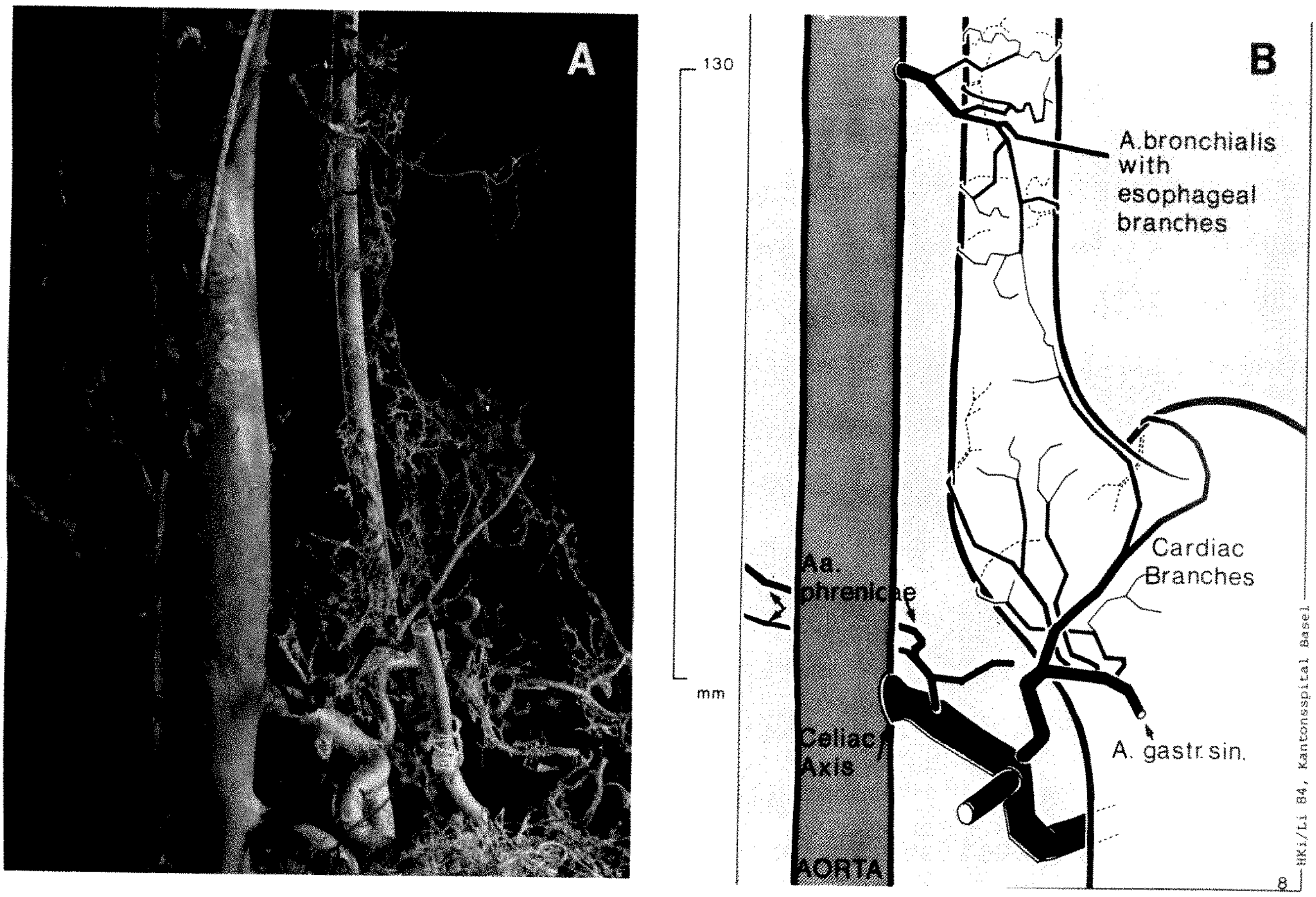
The esophagus ranged from 24 to 34 cm in length (cricoid to cardia) with an average of 27.6 cm. The mean distance between the celiac axis and the aortic arch was 23 cm in the postmortem specimen and this did not differ from the corrosion cast.

Corrosion Cast

The casts contained the complete arterial tree of the tongue, esophagus, stomach, greater omentum, and pancreas. The esophagus was easy to discern by virtue of the intraluminal tube placed at autopsy and by the tubular arrangement of its small vessels. These formed arterial anastomoses (Figs. 3 and 4) but often was incomplete in Beracryl casts because these casts did not display the fine arteriolae retae. The microvasculature was shown with the Mercox cast and found to be a dense network of minute arterioles located in the tela submucosa and tunica mucosa without any interruption throughout the esophagus (Fig. 5).

Cervical Esophagus

The blood supply of the upper esophagus was provided by branches from both the right and left superior and the inferior thyroid arteries (Fig. 6). Compared with the esophageal vessels, the superior thyroid arteries were rather larger caliber vessels, the right being 2.0 mm, the left 1.5 mm internal diameter at their origin. The esophageal branches were 2–3 cm in length before dividing in small branches. These branches ran to the lateral aspect of the esophagus and anastomosed anteriorly and posteriorly. In one of the 16 specimens there was one singular esophageal branch from the subclavian artery.



FIGS. 3A and B. Arterial tree of the middle and lower esophagus. Beracryl specimen. *A*. Corrosion cast, right lateral aspect with intraesophageal catheter (c). In this example, three stem vessels supplied the intrathoracic esophagus: the bronchial artery, the left gastric artery, and the splenic artery. All these gave rise to several small esophageal branches (<1 mm diameter). The inferior phrenic artery (fat arrows) arose from the celiac axis and supplied exclusively the diaphragm. Stumps of the intercostal arteries are seen alongside the aorta (small arrows) with no branches to the esophagus. *B*. The diagram simplifies the arterial distribution. The vessels supplying the posterior wall of the esophagus are shown as dotted lines.

Intrathoracic Esophagus

The caudal aspect of the aortic arch had up to four vessels of 1–2.5 mm diameter (Figs. 7 and 8). These mainly supplied the trachea, but gave off up to six small branches to the esophagus. Just below the arch, one unpaired artery of 1–3 mm caliber regularly arose from the anterior aspect of the aorta. This divided into one tracheobronchial and one or two small esophageal arteries 0.3–0.5 mm in diameter (Fig. 3). Additional unpaired small arteries arose at variable locations from the anterior wall of the aorta: seven casts had one, three casts had two such arteries, and six casts had none at all. The aortic arteries ran to the posterior aspect of the esophagus and were 1.5–6 cm apart. Although their caliber

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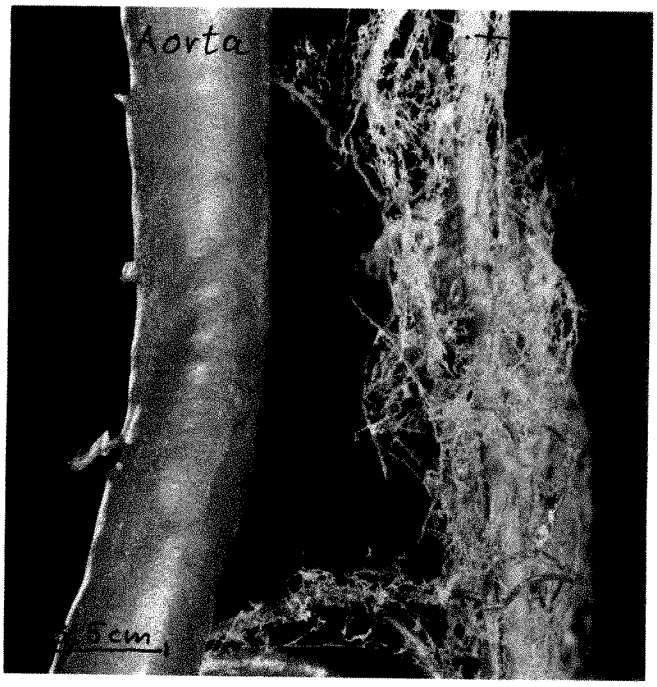
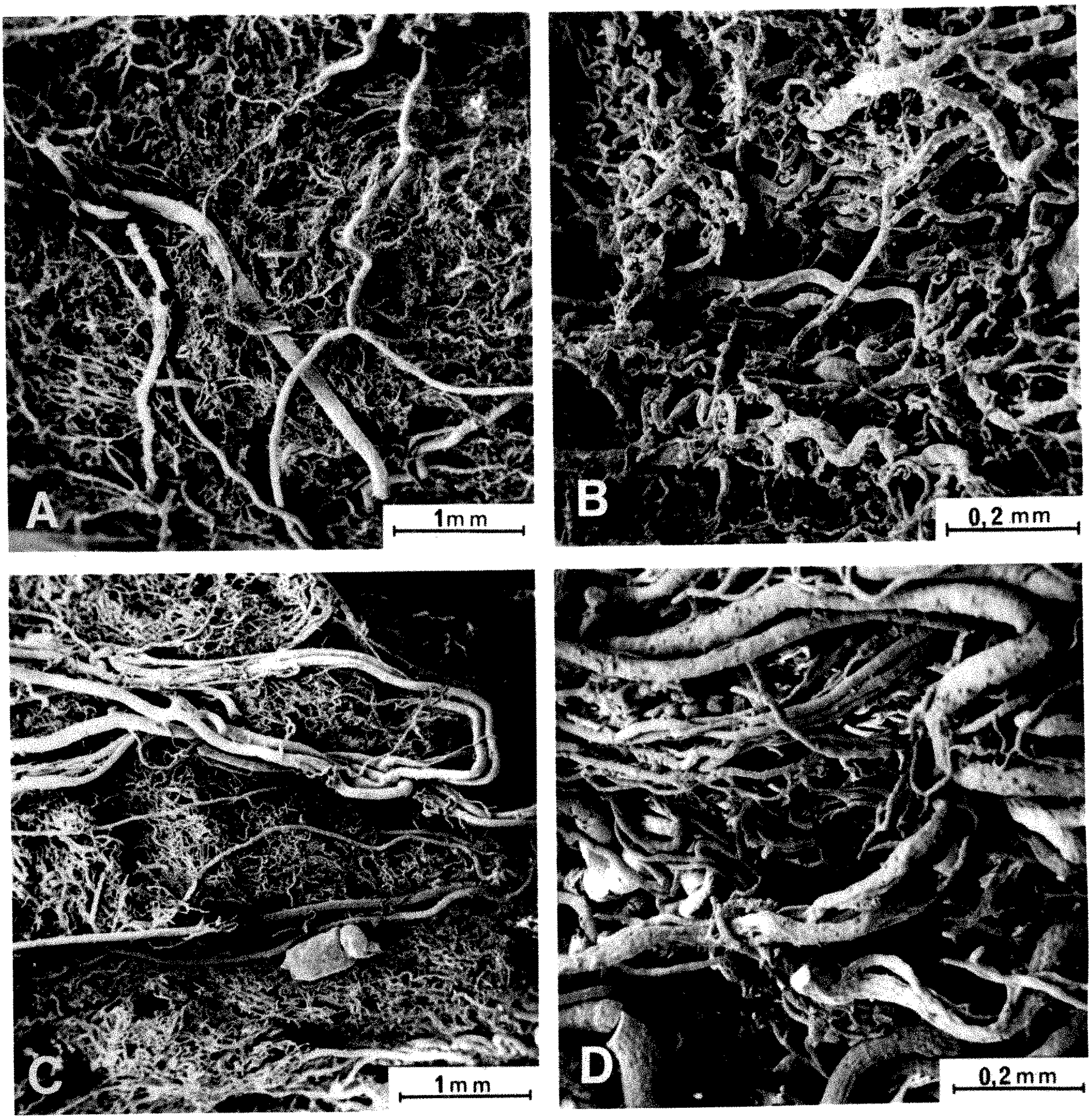


FIG. 4. Arterial vascularization of the middle and lower esophagus. Beracryl specimen, dorsolateral aspect with left gastric and splenic artery below and aortic vessel above. A catheter is still in place in the esophageal lumen. Note the small diameter of the esophageal vessels that divide into the microvascular submucosal network.



FIGS. 5A–D. Microvasculature of the esophagus. Mercox specimen. Scanning electron microscopy of complete vascular casts with arterioles, capillaries, and veins. *A* and *B*. 7-cm cranial of the cardia. *C* and *D*. at the cardia. Submucosal network at different magnifications viewed from the external aspect. The vessels form a polygonal meshwork overlying the mucosa (SEM by Dr. Düggelin, Basel).

ranged from 2.3–1.5 mm close to its aortic origin, all were divided and less than 1 mm at entering the esophageal wall (0.8–0.3 mm).

In 10 of the 16 specimens, complete rows of intercostal arteries with stumps of at least 1–4 cm in length were obtained. Only two of these had one small arterial branch to the esophagus, both arising from the fourth right intercostal artery.

Intra-abdominal Esophagus

The lower esophagus and the cardia were supplied by up to 11 larger caliber branches of 0.5–2 mm diameter originating from the left gastric artery (Figs. 3 and 8). Some of these arose close to the origin of the left gastric artery, and ran 2–3 cm alongside the right lateral aspect of the cardia before dividing into smaller branches.

These branches supplied the right lateral and anterior wall but only parts of the dorsal cardia and lower esophagus. The dorsal aspect of the cardia and lower esophagus was supplied by branches of the splenic artery *via* larger caliber fundal branches and numerous small fundal tributories. The left gastric artery and the splenic artery arose at variable location from the celiac axis (Fig. 9). A great variability was also seen with the origin of the inferior phrenic arteries (Fig. 10). These occasionally arose close to the left gastric artery; however, we never found any branch supplying the esophagus. Figure 11 summarizes the general pattern of the stem arteries and the vascular orientation in the esophagus.

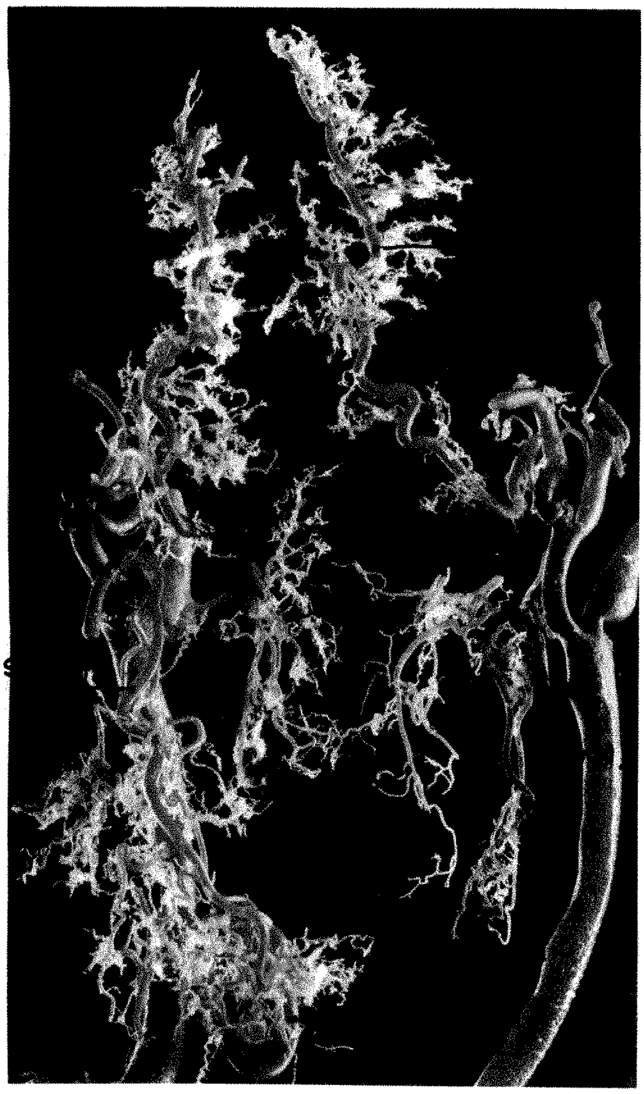


FIG. 6. Arterial cast of the cervical area and tongue with lingual artery (l.A.) from the anterior aspect. Beracryl specimen. The contours in the center show the esophageal arteries (e.A.) arising from the right and left superior thyroid arteries (S.th.A.) in this example. Both arose from the common thyroid artery (c.c.A.). The right branch of the superior thyroid artery descended and anastomosed with the right inferior thyroid artery (i.th.A.). This also gave off branches to the esophagus (e.A.).

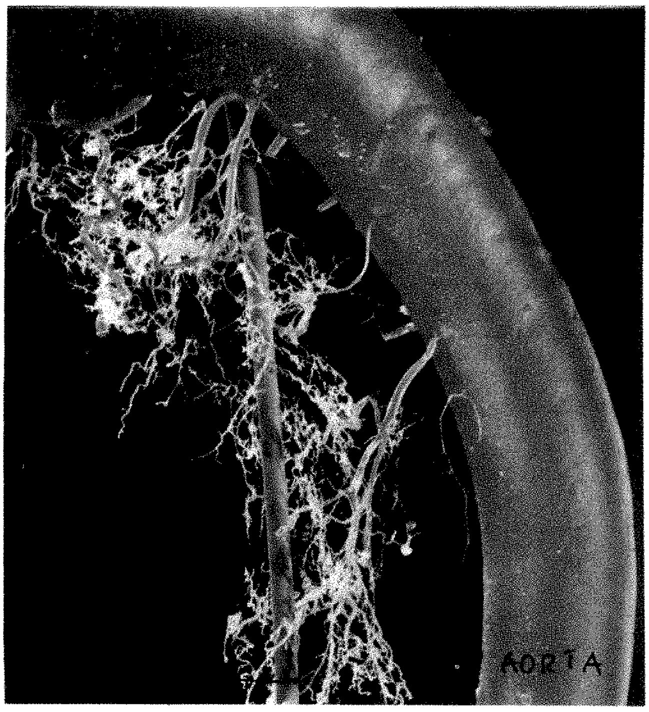


FIG. 7. Arterial cast (Beracryl) showing the bunch of tracheobronchial arteries. These arise from the aortic arch and give off multiple, very small branches (100–300 μm) to the esophagus. A catheter is still in place in the esophageal lumen. Left dorsolateral aspect.

Discussion

The rich but delicate vascularization of the esophagus is of concern in all surgery of this organ. There are, however, only a few original studies on the intimate vascular supply of the esophageal wall in humans. Some reports do not clearly indicate whether they relate to the human or the dog.

The three-dimensional display obtained with corrosion casts provided a reliable view of the arterial system. We took advantage of the two rather new, commercially available synthetic resins. Mercox crosses the capillaries and displays the complete arteriovenous network. Beracryl has a particle size of 150 μm and therefore limits its penetration to corresponding size arterioles without penetrating into the arteriolae retae and the venous side of the circulation. This eliminated time-consuming pruning. Shrinkage of the material was negligible. The vascular casts were moderately strong, rigid, and did not warp. Accurate and permanent mounting preserved the record.

The wide distribution of Beracryl with complete arterial architecture of the intestines suggested that firstly the interruption and secondly the poorer display of the arterial tree of the intrathoracic esophagus was not due to technical failure but to the small diameter of the periesophageal vessels. Injection with Mercox with its ex-

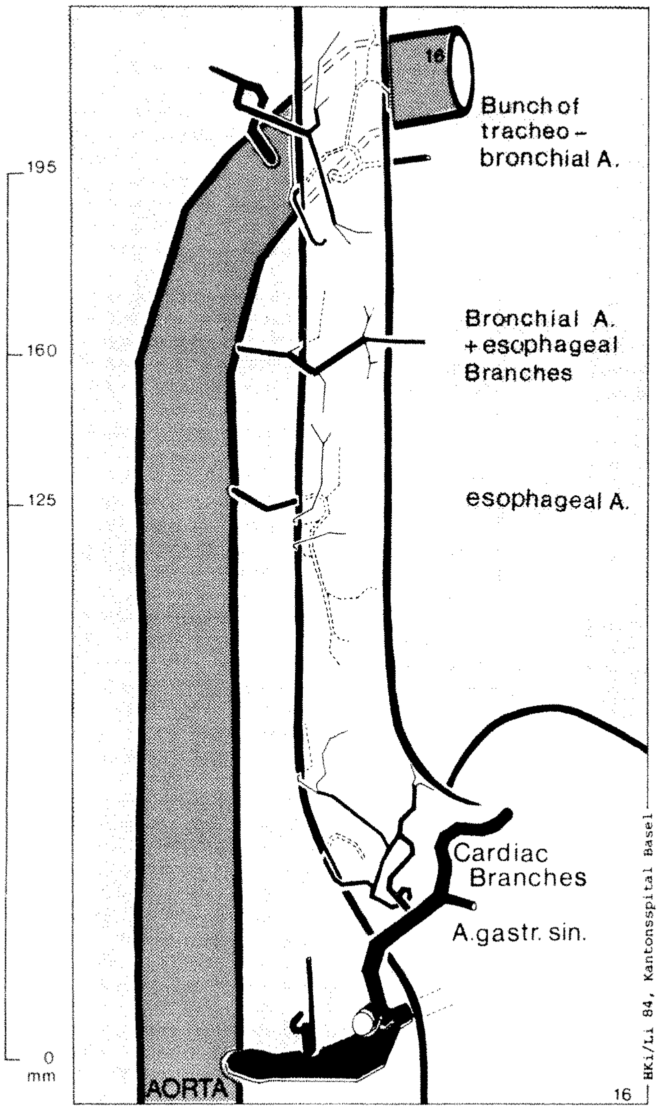

195
160
125
0
mm
16
Bunch of tracheo-bronchial A.
Bronchial A. + esophageal Branches
esophageal A.
Cardiac Branches
A.gastr. sin.
AORTA
16
HKi/Li 84, Kantonsspital Basel

FIG. 8. Diagram of the most common distribution of the arterial stem vessels and branches that supply the intrathoracic and abdominal esophagus in one of the specimens. Right lateral aspect with aorta untwisted. The arterial diameter is approximately in scale. The preferable site of surgical ligation of the left gastric artery is shown with an arrow. This retains some arterial supply to the esophagus.

tremely low viscosity documented that the esophageal branches were connected by a dense network of minute vessels located in the submucosa and mucosa. The evident continuity of the vessels and the rich anastomosing intramural vascularity explains why the mobilized esophagus retains an "excellent blood supply" over a long distance,[30] and why ligation of the left gastric artery most of the time does not compromise the surgical anastomosis. The extremely small caliber of the nutritional vessels, on the other hand, may also explain the failure of esophagointestinal anastomosis in case of any mechanical damage or disturbance of the microvascular circulation.

With respect to the upper third of the esophagus, we confirmed previous work[39–41] demonstrating rich supply from all of the thyroid arteries. Our main interest centered on the intrathoracic arterial supply. Our results explain the apparent paradox of relatively important arterial branches supplying the medial third of the esophagus leading to surprisingly moderate bleeding on blunt dissection. This paradox is explained by the fact that these arteries branch off into minute vessels in the periesophageal mediastinum before entering the esophageal wall. If, however, the tumor involves related structures, fatal bleeding from the azygos vein,[9,15,29] tracheal tear and pneumothorax,[5–7,15,31–33] and lesions of the recurrent nerve may occur.

With regard to the abdominal blood supply, branches of the left gastric artery as a third main source supplied both the lower intrathoracic and intra-abdominal esophagus and the cardia. In addition, we found that the posterior aspect of this area received an excellent blood supply from fundal branches or direct branches of the splenic artery.

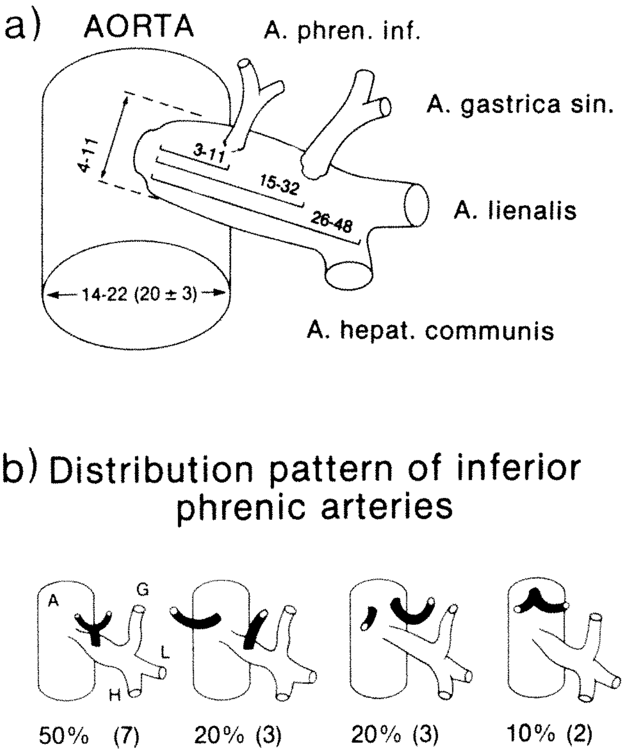


FIG. 9. Diagram of the celiac axis and its branches. a) The first branch was the inferior phrenic artery (A. phren. inf.) in 70%; second branch was the left gastric artery (A. gastrica sin.) in 100%. Finally, the celiac axis divided into the splenic artery (A. lienalis) and the common hepatic artery (A. hepat. communis). The site of arterial branching is given as range distance in millimeters from the origin of the celiac axis. b) The site of origin of the inferior phrenic arteries and their distribution in our specimens is shown. These vessels supplied only the diaphragm: none of our specimens had branches to the esophagus. A = artery, G = left gastric artery, L = splenic artery, H = common hepatic artery.

Branches from the right fourth and fifth intercostal arteries have been described in 25% of the cases.[19,21,22] In 10 specimens we found two small vessels from the fourth intercostal arteries, both of them supplying the tracheobronchial area giving off only minute branches, if any, to the esophagus. An extensive supply from many intercostal arteries, as often shown in textbooks, is true for the dog's esophagus[34-37] as we could confirm in four dogs with our technique, but not in humans.

Our findings also correct the unsubstantiated claim that caudal phrenic arteries play a role in esophageal vascularization.[19,22] In some of the specimens we found the origin of both phrenic and gastric arteries from the celiac axis being extremely close: larger caliber esophageal branches from the left gastric artery may have been erroneously taken for a phrenic artery in similar cases.

In conclusion, two points may be stressed on the basis of our findings: (1) The moderate bleeding observed after blunt esophagectomy is due to the fact that the nutritional arteries divide into minute branches within the periesophageal mediastinal tissue before entering the esophageal wall. The physiologic response of these small vessels to tearing is post-traumatic contracture with secondary thrombosis, hence hemostasis. (2) There are long segments of the esophagus supplied by dense vascular networks within the esophageal wall connecting the various vascular territories. They can compensate for the severance of one of the vascular sources. Rough manipulation of the organ may, however, easily compromise this intramural vascular network, thus jeopardizing surgical anastomosis with the stomach or gut regardless of the techniques applied.

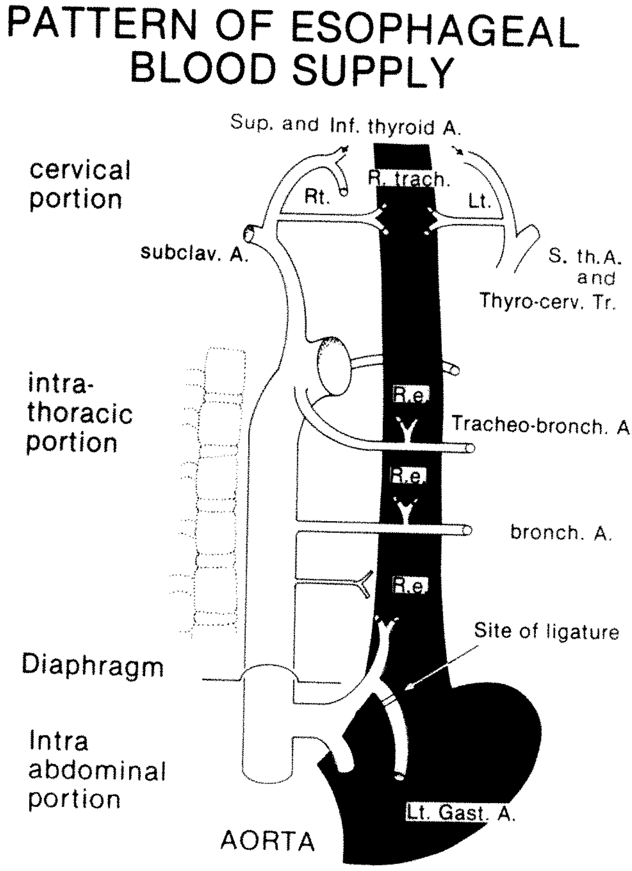


FIG. 10. This scheme summarizes the most common extraparietal sources of esophageal blood supply (stem vessels) and their topographical relations. All the esophageal branches (R.e.) arising from the stem vessels were extremely fine (100–500 μm). A = artery, Tr = trunc, Lt = left, Rt = right. The preferable site of surgical ligation of the left gastric artery is shown with an arrow.

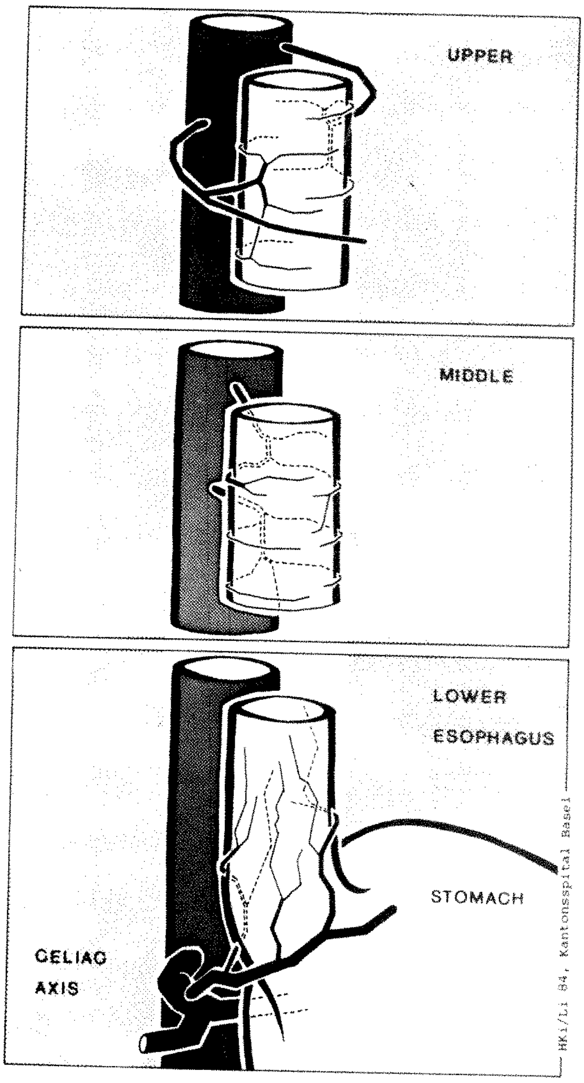


FIG. 11. Schematical representation of the vascular orientation. Smaller arteries run mainly horizontal in the upper esophagus and vertical to the axis in the lower esophagus. These arteries were complemented by the microvascular network that connected the arteries in the submucosa throughout the esophagus.

Our study does not allow any statement with regard to "oncological adequacy" of the blunt esophagectomy. Careful evaluation of this procedure for tumors restricted to the esophageal wall would seem worthwhile. It appears of particular interest in all patients having significant pulmonary disease.

Acknowledgments

We thank Professor Dr. R. Guggenheim and Dr. Düggelin, Institut für Rasterelektronenmikroskopie, Universität Basel, Switzerland, for their help with evaluation of the microcirculation. We also thank Professor Dr. Heitz and collegues of the Institute of Pathology for the autopsy material.

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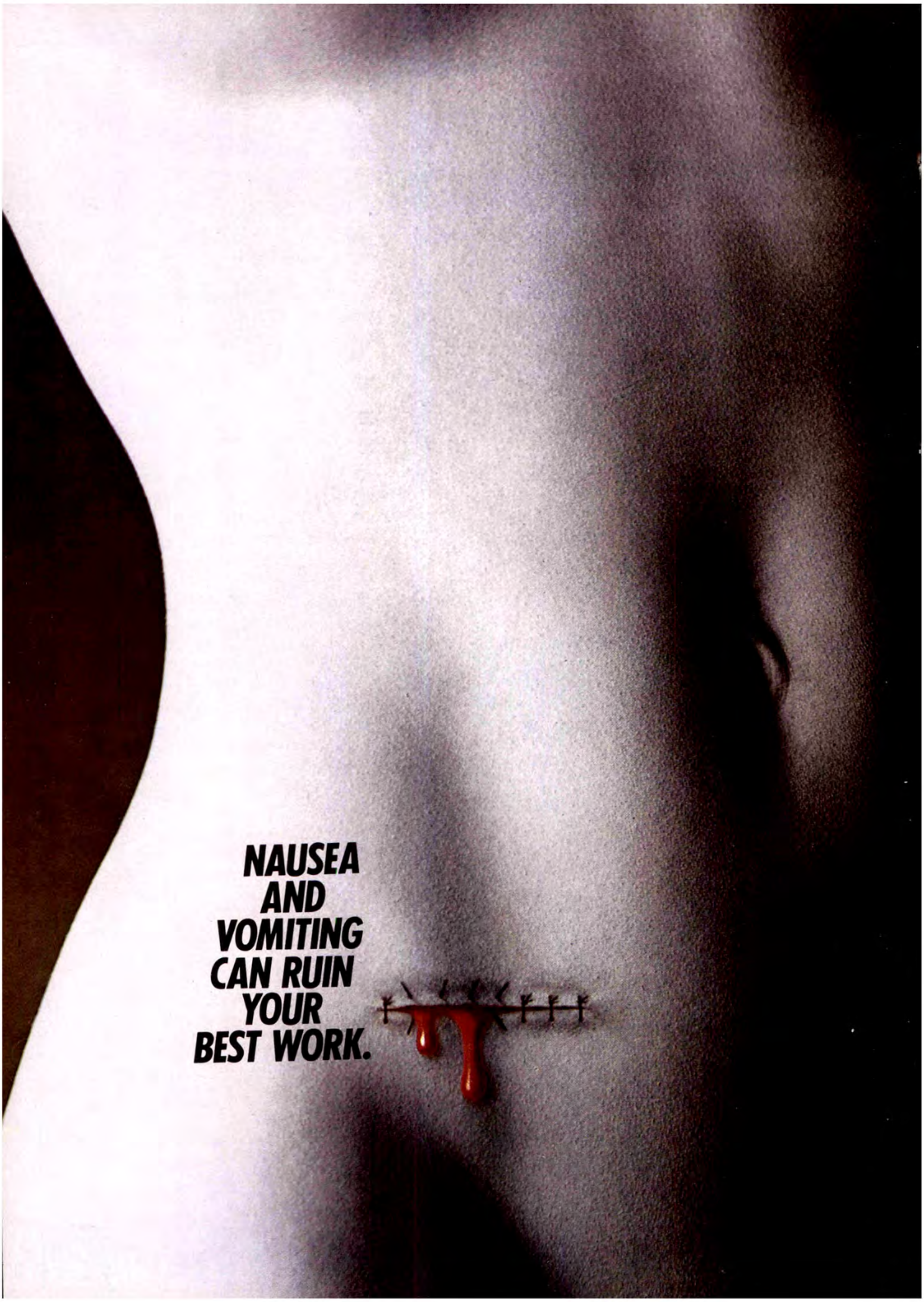
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Due to the difficulty in assessing addiction in patients who have recently received substantial amounts of narcotic medication, caution should be used in the administration of Stadol. Detoxification of such patients prior to usage should be carefully considered.

Use During Balanced Anesthesia: Since the combined respiratory depressant effect of all intravenous medication used during conduct of general anesthesia may lead to underventilation or apnea, butorphanol should be administered during balanced anesthesia only by persons specifically trained in the use of intravenous anesthetics and adjuncts, the maintenance of a patent airway and management of respiratory effects of all intravenous medication administered. An opioid antagonist, resuscitative and intubation equipment and oxygen should be readily available.

Drug Dependence: Special care should be exercised in administering Stadol to emotionally unstable patients and to those with a history of drug misuse. When long term therapy is contemplated, such patients should be closely supervised. Even though Stadol has a low physical dependence liability, care should be taken that individuals who may be prone to drug abuse are closely supervised. It is important to avoid increases in dose and frequency of injections by the patient and to prevent the use of the drug in anticipation of pain rather than for the relief of pain.

Head Injury and Increased Intracranial Pressure: Although there is no clinical experience in patients with head injury, it can be assumed that Stadol, like other potent analgesics, elevates cerebrospinal fluid pressure. Therefore the use of Stadol in cases of head injury can produce effects (e.g., miosis) which may obscure the clinical course of patients with head injuries. In such patients Stadol must be used with extreme caution and only if its use is deemed essential.

Cardiovascular Effects: Because Stadol increases the work of the heart, especially the pulmonary circuit, (see Clinical Pharmacology), the use of this drug in acute myocardial infarction or in cardiac patients with ventricular dysfunction or coronary insufficiency should be limited to those who are hypersensitive to morphine sulfate or meperidine.

PRECAUTIONS–Certain Respiratory Conditions: Because Stadol causes some respiratory depression, it should be administered only with caution and low dosage to patients with respiratory depression (e.g., from other medication, uremia, or severe infection), severely limited respiratory reserve, bronchial asthma, obstructive respiratory conditions, or cyanosis.

Impaired Renal or Hepatic Function: Although laboratory tests have not indicated that Stadol causes or increases renal or hepatic impairment, the drug should be administered with caution to patients with such impairment. Extensive liver disease may predispose to greater side effects and greater activity from the usual clinical dose, possibly the result of decreased metabolism of the drug by the liver.

Biliary Surgery: Clinical studies have not been done to establish the safety of Stadol administration to patients about to undergo surgery of the biliary tract.

Usage as a Pre-operative or Pre-anesthetic Medication: Slight increases in systolic blood pressure may occur, therefore caution should be employed when Stadol is used in the hypertensive patient.

Usage in Pregnancy: The safety of Stadol for use in pregnancy prior to the labor period has not been established; therefore, this drug should be used in pregnant patients only when in the judgment of the physician its use is deemed essential to the welfare of the patient.

Reproduction studies have been performed in rats, mice, and rabbits and have revealed no evidence of impaired fertility or harm to the fetus due to Stadol at about 2.5 to 5 times the human dose.

Usage in Labor and Delivery: Safety to the mother and fetus following the administration of Stadol during labor has been established. Patients receiving Stadol during labor have experienced no adverse effects other than those observed with commonly used analgesics. Stadol should be used with caution in women delivering premature infants.

Usage in Nursing Mothers: The use of Stadol in lactating mothers who are nursing their infants is not recommended, since it is not known whether this drug is excreted in milk. Stadol has been used safely for labor pain in mothers who subsequently nursed their infants.

Usage in Children: Safety and efficacy in children below age 18 years have not been established at present.

ADVERSE REACTIONS–The most frequent adverse reactions in 1250 patients treated with Stadol are: sedation (503, 40%), nausea (82, 6%), clammy/sweating (76, 6%).

Less frequent reactions are: headache (35, 3%), vertigo (33, 3%), floating feeling (33, 3%), dizziness (23, 2%), lethargy (19, 2%), confusion (15, 1%), lightheadedness (12, 1%).

Other adverse reactions which may occur (reported incidence of less than 1%) are:

CNS: nervousness, unusual dreams, agitation, euphoria, hallucinations, seizures
Autonomic: flushing and warmth, dry mouth, sensitivity to cold
Cardiovascular: palpitation, increase or decrease of blood pressure
Gastrointestinal: vomiting
Respiratory: slowing of respiration, shallow breathing
Dermatological: rash or hives
Eye: diplopia or blurred vision

OVERDOSAGE–Manifestations: Although there have been no experiences of overdosage with Stadol during clinical trials, this may occur due to accidental or intentional misuse as well as therapeutic use. Based on the pharmacology of Stadol, overdosage could produce some degree of respiratory depression and variable cardiovascular and central nervous system effects.

Treatment: The immediate treatment of suspected Stadol overdosage is intravenous naloxone. The respiratory and cardiac status of the patient should be evaluated constantly and appropriate supportive measures instituted, such as oxygen, intravenous fluids, vasopressors and assisted or controlled respiration.

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D. JAMES B. ST. JOHN, F.R.A.C.P.,§ and GEORGE MORSTYN, PH.D., F.R.A.C.P.*†

Fifteen patients with locally advanced esophageal cancer were treated with phototherapy. Each patient had dysphagia and weight loss before therapy and could not be operated on because of the extent of the tumor or poor performance status. Patients received a photosensitizer (hematoporphyrin derivative) 72 hours before phototherapy and were then treated by light delivered by an argon pumped dye laser or gold metal vapor laser at powers up to 2.2 W and doses of 337 J/cm^2. Fourteen patients received 24 treatments. The results were *all* patients achieved a tumor response. The depth of response depended on the dose and dose rate of radiation. There were four of 24 local complications (mediastinitis 3, bronchoesophageal fistula 1). These occurred in patients treated with a power of greater than 1.5 W. There were two complete pathologic remissions in patients with locally advanced cancer. In conclusion, phototherapy is an effective alternative to other forms of palliation and potentially may be an alternative to surgery in selected cases of locally advanced esophageal cancer.

TREATMENT OF CARCINOMA of the esophagus is unsatisfactory. Although there has been recent improvement in the survival of patients treated by surgical resection,[1] the survival of patients with inoperable cancer is poor. Furthermore, radiotherapy, chemotherapy, or dilation and intubation often do not provide good palliation. There have been several reports on the use of laser therapy for the creation of a larger esophageal lumen to enable patients to swallow. This has been achieved either by directly coagulating tumor with an Nd Yag Laser or by photodynamic therapy using an argon pumped dye laser emitting light of 630 nm onto tumors presensitized with hematoporphyrin derivative (HpD).[2-9]

From the Melbourne Tumour Biology Branch, Ludwig Institute for Cancer Research, Department of Surgery,† Department of Anatomical Pathology,‡ and Department of Gastroenterology,§ PO Royal Melbourne Hospital, Victoria, Australia*

HpD has been shown to selectively localize in many human and experimental tumors[4] and to sensitize them to kill by light of appropriate wavelength. Photodynamic therapy has been used to treat many human tumors, including recurrent breast cancer,[4] squamous carcinoma of the head and neck,[5] bronchial carcinoma,[6] gastrointestinal tract cancer,[7] and bladder cancer.[8] Complete and partial response rates of up to 60% have been reported in bronchial and gastrointestinal tract cancers. There have been two previous reports dealing specifically with esophageal cancer. McCaughan et al.[9] reported the results of 16 patients with advanced cancer and Hayata et al.[7] reported on the results of 12 patients with advanced cancer.

These studies have not attempted to identify the maximum tolerable dose of light for the phototherapy of esophageal cancer. Variable dose rates were used with powers of 90–400 mW and 200–1000 mW.[7,9] It is not clear whether dose rate is an important determinant of tumor kill, although it is clearly important for the kill produced by x-irradiation.[10] The dose of light delivered in one of the studies[7] was less than 150 J/cm^2; in the other study[9] insufficient information was provided to calculate the dose delivered.

The dosimetry in photodynamic therapy is poorly developed. Only the power output of the laser and the duration of therapy can be measured accurately. The surface area of the tumor can only be estimated and the delivery systems using fibers with a variety of tips provide variable distribution to the tumor. The absorbed dose of light cannot be measured. We describe a method

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TABLE 1. *Characteristics of Patients with Esophageal Cancer*

Patient	Age (years)	Sex	Histology	Site	Length (cm)	Extra-esophageal Spread	Prior Treatment	ECOG Status
1	66	M	SCC	Lower 1/3	10	Mediastinal/hepatic	Radiotherapy	2
2	61	F	Adeno	Lower 1/3	3	Mediastinal	Surgery	1
3	82	F	Adeno	Lower 1/3	4	Nodal	None	4
4	61	F	Adeno	Lower 1/3	8	Mediastinal	Surgery/tube	2
5	72	F	SCC	Mid 1/3	5	Mediastinal/nodal	Radiotherapy	2
6	78	M	SCC	Lower 1/3	10	Mediastinal/hepatic	None	2
7	65	F	SCC	Mid 1/3	5	Mediastinal	None	2
8	60	F	SCC	Upper 1/3	5	Mediastinal	Radiotherapy	2
9	82	F	SCC	Mid 1/3	8	None	None	2
10	80	F	SCC	Mid 1/3	8	Mediastinal	None	2
11	57	F	SCC	Mid 1/3	9	Mediastinal	Radiotherapy	2
12	82	M	Adeno	Lower 1/3	10	Mediastinal	None	3
13	72	M	Adeno	Lower 1/3	6	None	None	2
14	59	M	SCC	Mid 1/3	10	Mediastinal	Surgery	2

SCC = squamous cell carcinoma. ECOG = Eastern Clinical Oncology Group.

of applying light to an esophageal cancer that improves the accuracy of light delivery using a balloon filled with a light dispersing medium. We have undertaken a Phase 1 study of photodynamic therapy of advanced esophageal cancer using an argon pumped dye laser and a gold metal vapor laser. We have used high power levels up to 2.2 W and large doses up to 337 J/cm^2 to determine doses of light that are tolerable and whether the extent of tumor kill is dose related.

Patients and Methods

All patients gave informed consent before the study. Fourteen patients were admitted to the Phase 1 study. They were treated from March 1985 to September 1986. In the first half of the study patients were assessed as being unsuitable for any other form of therapy. In the second half of the study, photodynamic therapy was offered as an alternative to other forms of palliative therapy. The characteristics of the patients and tumor types are shown in Table 1. This study was approved by the Ethics Committee of the Royal Melbourne Hospital.

Technique of Photodynamic Therapy

An intravenous infusion of 2.5–5.0 mg/kg of HpD was administered to all patients 72 hours before laser therapy. HpD was obtained from the Pharmacy Department of Queen Elizabeth Hospital (Adelaide, South Australia) and was prepared by the acetylation of hematoporphyrin using the method described by Forbes et al.[11]

Hematologic and biochemical parameters were measured regularly after the infusion to assess and detect any toxic effects of the HpD. In five patients fluorescence was measured in the serum to assess peak levels and decay characteristics. Patients were screened from direct sunlight for up to 1 month. Laser light at 627–630 nm was generated using an argon pumped Rhodamine B dye laser (Spectra Physics, Model 164-05; argon laser, Model 375 dye laser, Spectra Physics, Mountain View, CA (9 patients, 16 therapies) or a gold metal vapor laser (Quentron, South Australia) (8 patients, 8 therapies). Light was delivered through a quartz fiber with a power output at the fiber tip varying from 0.5–2.2 W.

The quartz fiber was passed down a flexible endoscope (Olympus GIFQ, Olympus Optical Co., Ltd., Japan) and light directed towards the tumor. Eye protection was worn by the operator during this procedure.

To control the dose of light applied to the tumor, a light delivery system was devised as shown in Figure 1. This consisted of a polythene cannula with an attached thin-walled balloon that assumed an elongated shape measuring 8 × 1 cm in diameter when distended with 0.5% lipid emulsion (Intralipid®). The balloon was introduced into the lumen of the esophageal cancer *via* the fiberoptic endoscope after dilation of the cancer. With the balloon accurately in place within the tumor, the quartz fiber was moved from one end of the balloon to

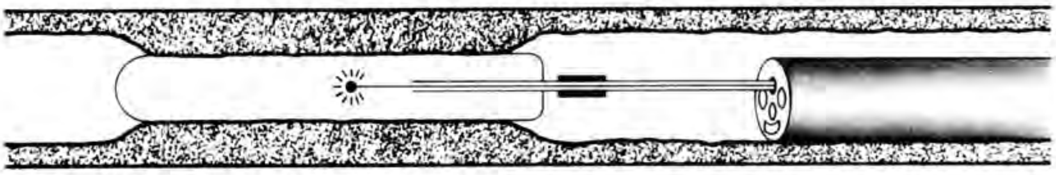


FIG. 1. Schema of delivering light to the tumor. The diagram shows the laser fiber in a balloon filled with Intralipid (0.5%) in the lumen of the esophagus.

TABLE 2. *Results of Photodynamic Therapy in Esophageal Cancer*

							Ability to Swallow					
Patient	HpD (mg/kg)	Power (W)	Total Dose J/cm^2	Total Dose (J)	Length (cm)	Type of Laser	Before Laser Therapy	After Laser Therapy	Duration of Response (wks)	Complications	Survival (wks)	Time in Hospital (days)
1	2.5	0.5	1800	60	12	C	1	3	14	Fever day 1, sunburn 2 wks	19	30
2	2.5	1	1740	129	3	C	2	4	17	Sunburn 8 wks		7
	5.0	0.7	2562	190	3	C	2	4	26	None		3
	5.0	2.0	5400	337	6	C	2	4	24	None	67	5
3	2.5	1.0	3600	150	8	C	1	3	28	None	28	6
4	2.5	1.0	3600	150	8	C	1	2	4	Sunburn 2 wks	25	10
	2.5	1.0	2040	85	8	C	1	2	4			8
5	5.0	1.0	3000	191	5	C	2	4	1	Fever day 1		14
	2.5	1.0	3600	229	5	C	2	4	13	Fever day 3	13	14
6	5.0	0.9	3240	103	10	C	1	2	1	None	21	15
	2.5	1.3	4758	151	10	C	2	3	21	Fever day 2		
7	5.0	1.0	3900	207	6	C	2	2	3	Pain, fever day 7		2
	5.0	0.7	2562	136	6	C	2	3	12	Pain, fever day 7	60+	7
	5.0	2.0	3840	245	6	P	2	2	8	Fever day 4, mediastinitis		28
8	5.0	1.0	3000	191	5	C	2	2	2	Fever day 1	12	30
	5.0	1.7	3296	210	5	P	2	2	4	Fistual day 39		
9	5.0	1.8	4752	198	8	P	4	2	2	Death day 10	1	10
10	5.0	1.5	3150	125	8	C	3	3	2	None		8
	5.0	2.2	4780	190	8	P	3	3	2	Fever day 3	10	8
	5.0	1.5	6039	192	10	C	3	3	6	None		21
11	5.0	1.7	5392	191	9	P	3	4	14	Fever day 4	14+	13
12	5.0	1.8	4633	150	10	P	4	2	6	Pain and fever, day 2, fistula, abscess day 40	6	42
13	5.0	1.8	3098	155	6	P	3	2	3	None	5+	21
14	5.0	1.8	2181	72	10	P	4	4	2	Fever, pain day 10	4+	16

Dysphagia score:
1 = total obstruction.
2 = fluids.
3 = vitamized food.
4 = soft diet.
5 = normal.
C = continuous wave argon pumped dye laser.
P = pulsed gold metal vapor laser.

the other within the esophageal cancer resulting in light delivery to the whole tumor. The dosimetry was calculated assuming that the tumor was a cylinder with a diameter of 1 cm after the balloon was inflated within the lumen of the tumor. The length was determined by prior endoscopy. Doses of light between 60 and 337 J/cm^2 of tumor were delivered. This necessitated treatment times of 30–60 minutes. All patients in this series were treated under general anesthesia.

Assessment of Tumor Response

Before the laser therapy all the patients had endoscopic examination, the tumors were biopsied, photographed, and dilated if necessary, and the length of the tumor was measured. Barium meal and computed tomographic (CT) examinations of the thorax were obtained before treatment and 1 month after treatment. After laser therapy all patients had endoscopic examination at 48 hours and further photographs and biopsies were taken. This procedure was repeated 1 week and 2 weeks after therapy and when new symptoms such as dysphagia developed.

Results

The characteristics of the patients with esophageal cancer are shown in Table 1. Of the 14 patients, five had an adenocarcinoma and nine had a squamous cell carcinoma. Seven patients had lower-third tumors, six had mid-third tumors, and one had an upper-third tumor. Six patients had previous treatment, either radiotherapy or surgery. Twelve patients had advanced local mediastinal spread, and two patients had disease apparently confined to the esophagus on CT scan. All patients were deemed inoperable due to their clinical status or the stage of their tumor.

The details and results of the laser therapy are shown in Table 2. A total of 24 laser therapies were given to the

14 patients. In seven treatments, HpD was given at a dose of 2.5 mg/kg; in an additional 17 treatments, HpD was given at a dose of 5 mg/kg.

The gold metal vapor laser was used in eight of the 24 laser treatments. The mean power output at the fiber tip with this laser was 1.8 W (range: 1.7–2.2). The mean power output at the fiber tip of the argon pumped dye laser was 1.0 W (range: 0.5–2.0). The mean total dose of light was 3582 J (range: 1800–6039). The mean dose/cm^2 of tumor was 168 J/cm^2 (range: 60–337).

The degree of necrosis of the cancer after laser therapy was estimated by visual grading of the macroscopic appearance of the tumor at the postlaser endoscopic examinations. The necrosis was graded as follows: G0: no tumor necrosis visible; G1: tumor necrosis but obvious viable tumor persisting (Fig. 2); G2: apparent total tumor necrosis (Fig. 3); G3: total tumor necrosis with a physical appearance of esophageal tumor slough (Fig. 4).

The relationship between tumor necrosis (G_0–G_3) and light dose and power output of the laser is shown in Figure 5. G_1 minimal tumor necrosis correlated significantly with the dose of light (Spearman rank correlation test, correlation coefficient 0.368, $p = 0.04$) G3 esophageal tumor slough correlates significantly with a power output of the laser of >1.5 W (Spearman rank correlation test, correlation coefficient 0.54, $p = 0.005$).

The palliation of the symptoms produced by the tumors was assessed by measuring the improvement of dysphagia after therapy (Table 2).

The ability to swallow was assessed before laser therapy and 2 weeks after laser therapy using a dysphagia scale, and all patients achieved measurable improvement in the severity of dysphagia. The duration of the response varied from 1 to 28 weeks with a median of 9.5 weeks. With respect to weight changes, seven of the 14 patients maintained their weight from the time of laser therapy to 1 month after the therapy despite a history of loss of weight in the 3 months before treatment. The remainder of the surviving patients showed modest declines in weight.

The in-hospital mortality rate was 14% with two patients dying after their therapy, both aged over 80 years. One of these patients was shown at postmortem examination to have complete necrosis of the esophageal cancer but also significant esophageal wall necrosis associated with thrombosis of an esophageal artery (Fig. 6). In this instance cardiac arrest occurred 13 days after therapy and the postmortem examination showed significant coronary artery disease. The second patient in whom bronchoesophageal fistula pneumonia developed died 4 weeks after the therapy, and at postmortem examination had an extensive esophageal and mediastinal tumor with massive necrosis of the esophageal portion of the tumor.

Survival Data

A number of complications occurred after the therapy and are listed in Table 2. Febrile episodes were common but settled with the institution of antibiotics. In one patient mediastinitis developed with pleural effusions demonstrated on CT scan. This patient was treated conservatively with full recovery and subsequently had a strictured area of the esophagus resected (8 months after laser treatment). Histologic examination of the specimen revealed complete eradication of the esophageal tumor with a dense fibrous scar formation. There has been no recurrence of tumor 1 year later. This patient had heavy irradiation to the neck and esophagus for a paraesophageal tumor 10 years before the development of the presumed radiation-induced proximal esophageal cancer.

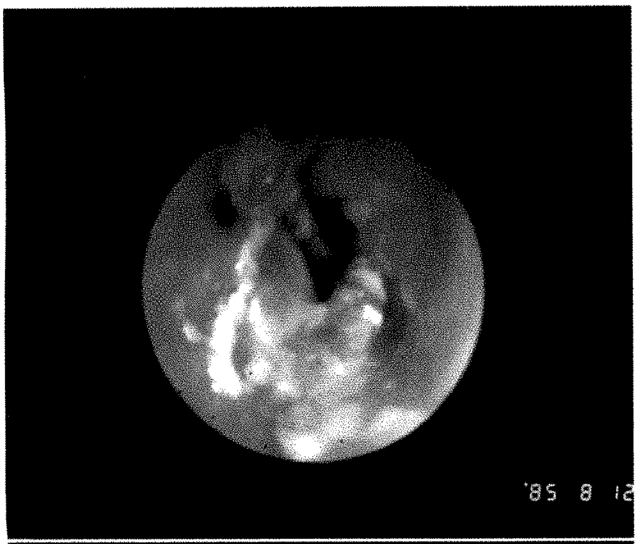
A laser power output of >1.5 W correlated significantly with the development of complications.

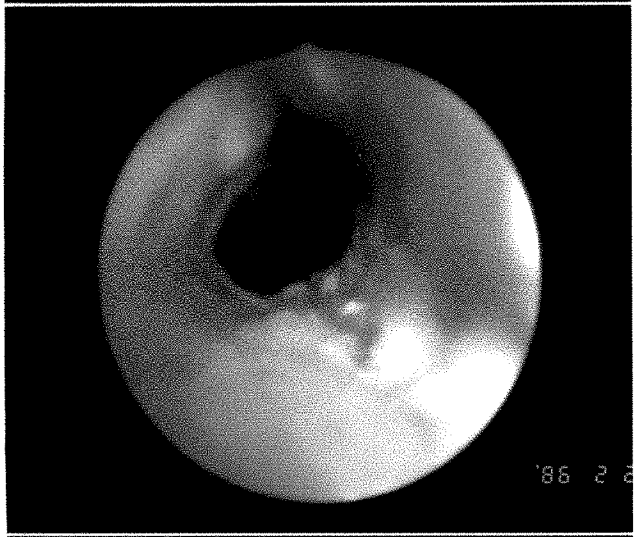
All patients received instructions to avoid direct sun. However, three patients showed a reaction to sunlight when inadvertently exposed. In two of these patients, their skin reaction developed in the hospital from light coming through the windows. In another patient, sun sensitivity developed after leaving the hospital. It was evident that this phenomenon of sun sensitivity persisted for several months after the therapy, and in one patient skin pigmentation developed that persisted for more than 6 months before fading. The basis for prolonged skin sensitivity is not clear. However, Figure 7 shows that HpD fluorescence can persist in the serum for up to 1 month. Similar findings were found in four other patients. There was no effect of HpD on liver or renal function as measured biochemically. To determine the effect of phototherapy on survival we compared the actuarial survival of all 14 patients with a previous series of patients treated for palliation nonsurgically (Fig. 8).[1] This survival has been stable in the hospital for 5 years. There was no significant difference between the curves.

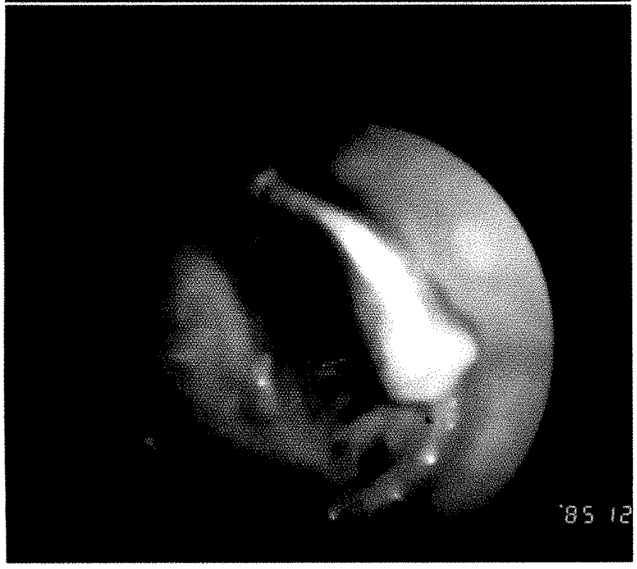
Discussion

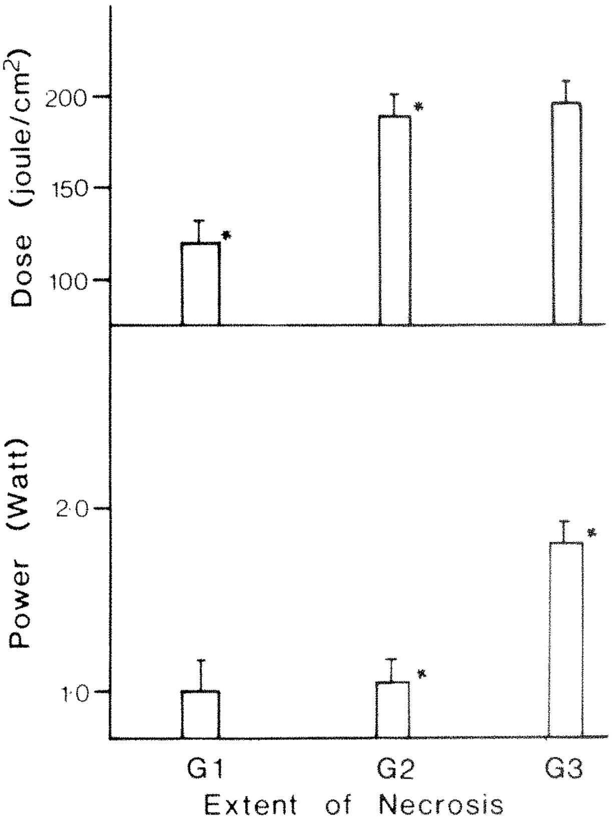
This study confirms that photodynamic therapy is an effective form of local therapy for esophageal cancer. All tumors treated showed some evidence of necrosis. In this group of patients there was no apparent difference in the response of squamous and adenocarcinomas.

This form of therapy produced reasonable palliation in patients who were close to having or had complete obstruction. The degree of palliation appeared to be at least as good as that produced by other forms of therapy. The eventual place for photodynamic therapy as a palliative treatment of advanced esophageal cancer is still to be established. It is likely that certain groups of pa-









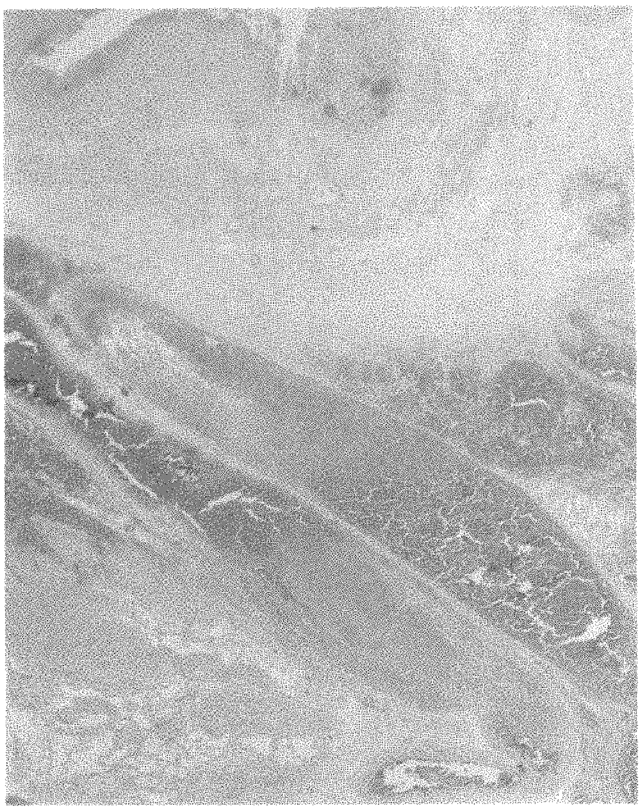


FIG. 2. *Top left.* G_1: minimal necrosis with macroscopic viable tumor. FIG. 3. *Middle left.* G_2: intermediate necrosis: macroscopic total tumor necrosis. FIG. 4. *Bottom left.* G_3: maximal necrosis: esophageal slough. FIG. 5. *Top right.* Extent of macroscopic tumor necrosis as a function of dose of light and power output of laser. Points of significance ($p < 0.05$) marked with asterisks. FIG. 6. *Bottom right.* Thrombosis of esophageal artery and vein after photoirradiation therapy.

tients will be better treated with this form of therapy than others. Further studies are needed to compare the various methods of palliation.

Of particular interest is the ability of photoirradiation therapy to produce complete eradication of local tumors. There are reports in the literature of the complete eradication of early esophageal and gastric cancers by photodynamic therapy.[6,7] This study includes the first cases of locally advanced esophageal cancer where local eradication of tumors has been obtained. Both patients had squamous carcinomas in the mid-esophagus with no prior therapy. One patient has had complete eradication proven by resection of a persisting stricture after the development of esophageal slough (grade G3). This patient had a locally advanced tumor on the basis of thickening in the mediastinum on CT scan but poor pulmonary function, and frailty initially precluded surgery. The patient received two treatments with the argon pumped dye laser with fairly rapid recurrence of the tumor. After a third treatment with the gold metal vapor laser mediastinitis developed and the patient required respiratory support for 5 days and drainage of pleural effusions. She recovered after this therapy but a persistent esophageal stricture developed that became difficult to dilate. There were problems with endoscoping this patient and it was elected to risk resection of the stricture. At the time of resection a benign stricture was discovered and histologic examination confirmed the complete absence of local tumor. The area in which the

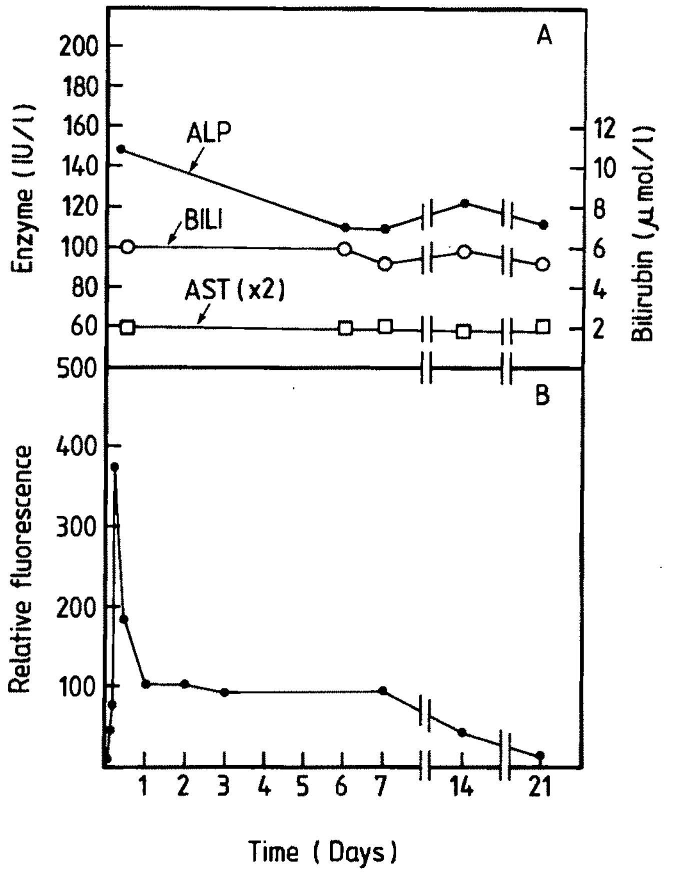


FIG. 7. Blood levels of photosensitizer and biochemical parameters in a patient receiving 5 mg/kg of hematoporphyrin derivative.

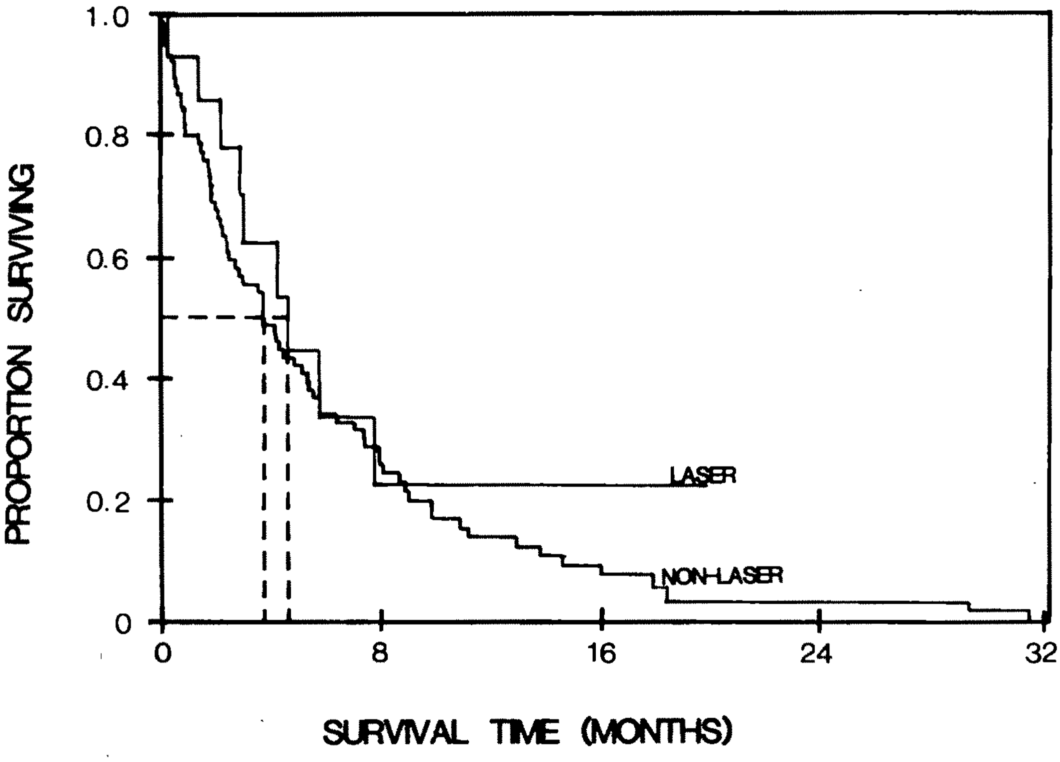


FIG. 8. Survival of all photoirradiation patients (laser) compared with patients treated for palliation before availability of photoirradiation.

tumor was previously noted was surrounded by a dense scar surmounted by a small shallow ulcer. This patient has remained tumor free for more than 12 months. The second instance where complete eradication was seen occurred in one patient who died 14 days after therapy and in whom at autopsy there was total necrosis of the tumor.

The ability to produce local eradication of advanced tumors raises the possibility of developing this form of therapy as a first-line form of treatment for Stage 1 esophageal cancer. However, increasing the effectiveness of the local therapy in this situation demands the development of techniques to support both the patient and the esophageal wall during the postoperative period when tumor necrosis is maximal and the repair processes have not developed sufficiently to maintain the integrity of the esophageal wall. Appropriate management may require antibiotics, nil by mouth, parenteral nutrition, and occasionally temporary intubation to splint the esophagus. This introduces a new dimension in the field of surgical oncology rather akin to the problems seen in the use of chemotherapy without surgery in lymphomas affecting the gastrointestinal tract to avoid perforation.

An important attribute of photodynamic therapy previously reported is the selectivity of cell damage. In this group of patients, however, it was evident that the selectivity was not absolute. There was generally a sharp demarkation between tumor necrosis and the proximal esophageal mucosa. However, in both the resected case and the autopsy specimen there was evidence of normal tissues deep to the tumor or close to the tumor showing necrosis. The histologic changes were characteristic after phototherapy with severe fibrinoid necrosis noted in blood vessels close to the tumor. This would suggest that a vascular phenomenon was significant in producing at least part of the necrosis. This may also be a factor in producing the damage to the normal esophageal wall. These vascular changes can resolve as was evident from the resected specimen of the eradicated cancer where recanalization of previously thrombosed vessels was seen. A vascular basis for the damage induced by phototherapy has previously been suggested based on *in vivo* experiments in small animals.[12]

A major problem with the assessment of the effectiveness of photodynamic therapy relates to the difficulties with dosimetry. Although the balloon system as described improves light delivery to the tumor, there may still be variation in the dose of light delivered to various parts of the tumor and the problem of a geographic miss also exists. This lack of precision makes it difficult to define the optimal doses of light for various tumors. In this study substantial variations in the dosage of light to the various areas of the tumor may have been responsible for variations in necrosis in various parts of the tumor. However a direct dose-response relationship was demonstrated in this study by comparing very low doses with higher doses of light. Extent of tumor necrosis also correlated with the presence of significant complications and occurred where the pulsed laser was used with a power output of greater than 1.5 W. There is an obvious need to clarify the problem of dose response. Our data suggest that for the therapy of esophageal cancers, lasers with a higher power may not be necessary since a limit determined by normal tissue tolerance may have been reached.

There is no systemic toxicity from phototherapy apart from the problem of sun sensitivity. This was found to be a persistent problem extending for 2–3 months from the time of laser therapy, and in some patients was associated with mild skin pigmentation. The development of photosensitizers with a shorter half-life would reduce this problem.

Acknowledgments

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Blunt Thoracic Trauma

Analysis of 515 Patients

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A retrospective analysis of 515 cases of blunt chest trauma is presented. The overall thoracic morbidity rate was 36% and mortality rate was 15.5%. Atelectasis was the most common complication. Severe chest trauma can be present in the absence of rib or other thoracic bony fractures. Emergency thoracotomies for resuscitation of the patient with blunt chest trauma with absent vital signs proved unsuccessful in 39 of 39 patients. A high index of suspicion for blunt chest injury occurring in blunt trauma, coupled with an aggressive diagnostic and therapeutic approach, remains the cornerstone of treatment to minimize the morbidity and mortality of such injuries.

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TRAUMA IS THE THIRD leading cause of death in the United States and the leading cause of death in persons under the age of 40. Twenty-five per cent of the 100,000 annual civilian traumatic deaths result from chest trauma.[1] Blunt thoracic injuries are more common than penetrating chest trauma, with the most frequent causes being motor vehicle accidents, falls, and crush injuries.[2]

The Shock Trauma Center of the Maryland Institute for Emergency Medical Services Systems (MIEMSS) is a 107-bed trauma referral center for the State of Maryland, serving a large population of patients with multisystem injuries, both acutely injured patients and traumatized patients referred from regional trauma centers. Seventy-five per cent of the admissions arrive by helicopter and 25% arrive by land transportation.

Between January 1982 and December 1984, 5378 patients were admitted to the MIEMSS Shock Trauma Center. We present a retrospective report on the MIEMSS experience with 515 patients who sustained blunt thoracic trauma within this 3-year period, including an analysis of the injury patterns, complications, and mortality for this group.

Materials and Methods

Five hundred fifteen patients were admitted to the MIEMSS Shock Trauma Center with blunt chest trauma between January 1982 and December 1984. The mean age was 36.9 years, with a range of 14–86 years. There were 374 males and 141 females admitted, constituting a male to female ratio of 2.7 to 1. The causes of these injuries encompassed automobile (70.9%), pedestrian (9.5%), and motorcycle accidents (7.8%); falls (7.6%); and miscellaneous causes (4.2%) (Table 1). Our miscellaneous category included injuries such as waterskiing accidents, assaults, farm accidents, a plane crash, and one person kicked by a horse.

Of the 515 patients, admission vital signs were available for 512 patients. Three hundred thirty-nine patients (66.2%) arrived with stable vital signs (defined as systolic blood pressure greater than 90 mmHg). One hundred forty-three patients (27.5%) had hypotension (defined as systolic blood pressure less than 90 mmHg). Thirty patients (5.7%) arrived with no pulse or blood pressure and with cardiopulmonary resuscitation in progress. The three patients whose admission vital signs were not available all died within 48 hours.

Results

The majority of patients with blunt chest trauma had an array of associated injuries. Although only 84 patients (16.3%) had isolated thoracic injuries, 431 patients (83.7%) had extrathoracic injuries. The magnitude of injury is further highlighted by the fact that nearly half (245) of these patients (47.5%) had two or more systems involved besides the thoracic injuries. The asso-

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ciated injuries included head trauma in 222 patients, extremity fractures in 205 patients, intra-abdominal injuries in 147 patients, and miscellaneous injuries in 181 patients. The miscellaneous category included spine injuries, pelvic fractures, facial trauma, and significant soft tissue injury.

Fractures of the Bony Thorax

Blunt thoracic trauma is often heralded by fractures of the bony thorax. These fractures reflect the large amount of energy that has been imparted to the chest wall and thoracic viscera (especially when the scapulae and sternum are involved). Recognition of these injuries is critical in the management of these patients. Rib fractures interfere with ventilation and may lacerate underlying lung parenchyma. Sternal and rib fractures may contribute to paradoxic chest wall motion and impair ventilation in that manner. If a scapula is fractured, high energy transfer has occurred to the thorax, and one must suspect that deeper structures have been injured.

Fractures comprised the largest single group of thoracic injuries in our series. There were 451 fractures of the ribs, scapulae, sternum, and clavicles either alone or in combination in 388 patients. Of these, rib fractures predominated (368), with nearly half of these involving three or more ribs. There was an 8% incidence of bilateral rib fractures. The remaining injuries comprised 14 sternal fractures, 43 clavicular fractures, and 25 scapular fractures. One hundred twenty-seven patients had no radiographic or clinical manifestations of bony thorax fractures despite the presence of other thoracic injuries.

Chest Injuries in the Absence of Fractures of the Bony Thorax

Bony fractures of the thorax (including ribs, clavicle, scapula, and sternum) are the most common injuries in blunt thoracic trauma and often are a hallmark of severe underlying injury. However, we have identified a group of patients with significant thoracic injuries in the absence of bony fractures. From our total group, we identified 127 (24.7%) such patients (Table 2); the majority of these injuries represented hemothoraces or pneumothoraces (62.2%). Nine of 19 ruptured thoracic aortas and 10 of 23 ruptured diaphragms were included in this group. Because the energy of forces is not dissipated by the fracturing of bones, other structures within the chest may become more vulnerable to injury. It is evident from this series that major thoracic blunt trauma cannot be ruled out in the absence of bony injuries.

Pneumothorax-Hemothorax

Pneumothorax is a frequent finding in blunt chest trauma. It is usually due to a rib fracture that is driven inward and damages the pulmonary parenchyma or to chest decelerating injuries, causing an abrupt increase in intra-alveolar pressure. Other causes of pneumothorax include a tear in the tracheobronchial tree or esophagus.[3]

TABLE 1. *Mechanism of Injury*

	No. of Patients	%
Automobile	365	70.9
Pedestrian	49	9.5
Motorcycle	40	7.8
Falls	39	7.6
Miscellaneous	22	4.2

Hemothorax often accompanies pneumothorax, with similar etiologies causing a tear in the blood vessels of the lung parenchyma, injury to intercostal vessels, or injury to the heart and great vessels.

Pneumomediastinum and pneumopericardium in the adult trauma patient are often incidental findings of air that has tracked along the bronchial or vascular sheaths of the thorax into the mediastinum and pericardium. Occasionally, this can be a grave sign of a ruptured bronchus or esophagus, uncontrolled pneumothorax, or ventilator barotrauma. Air within the pericardial space can develop into cardiac tamponade.[4]

In our series, 287 patients had complications of pneumothorax, hemothorax, or a combination of the two injuries. Of the 95 patients with pneumothoraces, 54 had simple pneumothoraces, 15 had bilateral pneumothoraces, eight had a tension pneumothorax, and one had an open pneumothorax. There were 17 patients in whom delayed pneumothoraces developed (defined as a pneumothorax occurring 24 hours after injury). Of the hemothorax group (193 patients), 54 patients had unilateral hemothoraces, 17 had bilateral hemothoraces, and 11 had delayed hemothoraces. One hundred eleven patients had various combinations of hemopneumothoraces.

In three of the six patients in whom pneumomediastinum developed, the condition was associated with car-

TABLE 2. *Chest Injuries in the Absence of Bony Thoracic Injury (N = 127)*

	N
Hemopneumothorax (unilateral, bilateral)	44
Pulmonary contusion (unilateral, bilateral)	35
Cardiac contusions	20
Ruptured diaphragms	10
Ruptured aortas	9
Cardiac rupture	4
Tracheobronchial injury	2
Pulmonary laceration	2
Great vessel injury	1

diac compromise due to tension pneumopericardium. Two patients had pneumomediastinum without pneumopericardium, and one patient had asymptomatic combination pneumomediastinum pneumopericardium.

Ruptured Diaphragm

Traumatic rupture of the diaphragm is a relatively rare finding in patients with blunt trauma. It is most commonly the result of motor vehicle accidents and is secondary to abrupt increases in intra-abdominal pressure. The injury usually occurs through the weakest points of the diaphragm, which are in the posterolateral positions along the embryonic fusion lines. However, diaphragmatic rupture has occurred in all areas of the diaphragm.[5] In previous series, right-sided diaphragmatic ruptures have been reported only rarely.[6] However, as this entity is more aggressively identified, right-sided lesions are being more frequently recognized.[7] Mortality is directly related to associated injuries.

We report on 23 cases of ruptured diaphragms: 16 (69.5%) were left sided and seven (30.5%) were right sided. Motor vehicle accidents were responsible for 78.0% of the injuries. Other causes included motorcycle accidents, pedestrian accidents, and a kick from a horse. In two cases (1 right and 1 left), diagnosis was delayed more than 1 week after injury. Of the patients with ruptured diaphragms, 14 (60.9%) had two or more systems involved, and the mortality rate was 26.9% (6 deaths). All injuries were repaired *via* abdominal incisions.

Aortic Ruptures

Traumatic thoracic aortic tears are one of the most catastrophic injuries seen in blunt chest trauma. The severity of such an event is appreciated when survival statistics are examined. A large, widely quoted study by Parmley has shown that only 20% of patients with aortic rupture survive for more than 1 hour after injury; 80% of patients die at the scene.[8] In initial survivors, if the injury is not surgically addressed, 40% die within 24 hours and 90% are dead by 10 weeks.

Nineteen patients presented to the MIEMSS Shock Trauma Center with a traumatic ruptured thoracic aorta; there were seven long-term survivors. As with the rest of the MIEMSS population, motor vehicle accidents were the predominant cause of injury and multiple injuries were present. Forty-four per cent of the patients had two or more extrathoracic systems involved. The mean age of this group was 42 years, with a range of 16–82 years.

Twelve patients with ruptured aortas died. Three of these patients presented in cardiac arrest. Two patients were in profound shock and had emergent thoracotomies, which disclosed free rupture of the aorta. Of these five deaths, aortic reconstruction was not attempted because of cardiac arrest. There were three late deaths not related to the aortic injury or perioperative course. One death was due to a presumed pulmonary embolus, and one was due to acute respiratory distress syndrome (ARDS) and sepsis. One patient died of an aortic esophageal fistula.[9] Four patients died of factors directly related to their aortic injury and repair. One of the seven survivors had a postoperative paraplegia develop. The total survival rate was 37% and the mortality rate directly related to aortic repair was 21%.

Tracheobronchial Injuries

Rupture of the thoracic tracheobronchial tree is a rare but serious injury in blunt trauma.[10] Kirsh and Sloan[6] have proposed three theories as to the cause of the injury. The first theory states that forceful compression to the thorax pulls each lung apart, with the resulting traction on the trachea and carina producing a tear. A second theory states that high intrabronchial pressure secondary to a closed glottis makes the tracheobronchial tree vulnerable to injury with sudden impact to the chest. A third theory is based on shearing forces on the tracheobronchial tree between the relative stationary areas of the cricoid cartilage and carina with decelerating forces.

Because many persons with disruption of the tracheobronchial tree do not survive, a true incidence of this injury is difficult to determine. In our series, we limited our reporting to the tracheobronchial injuries confined to the thorax and had four such patients. Of these patients, three had tracheal injuries within 2 cm of the carina and one had a mainstem bronchial tear. Three tears were primarily repaired, and one injury consisting of a small carinal tear was treated with expectant observation. Three of the four patients had injury of two or more extrathoracic systems. Two deaths occurred during initial resuscitation (within 6 hours of injury) and were due to multiple injuries. One survivor subsequently had bilateral pleural empyemas develop and the other patient had tension pneumopericardium develop that was treated by open pericardial drainage.

Flail Chest: Pulmonary Contusion

Crushing chest wall injuries resulting in flail chest most commonly occur from motor vehicle accidents; however, they are also associated with compression injuries, falls, and direct blows. The injury causes multiple fractured ribs, creating a segment of chest wall that has lost its continuity with the remainder of the thorax. This produces the paradoxic respirations that are frequently present with flail chest. Flail chest constitutes a serious chest wall injury, and its high morbidity and mortality are mainly due to underlying pulmonary injury and associated injuries.

Pulmonary contusion, defined as injury to lung parenchyma resulting in edema and interstitial hemorrhage, usually is the result of acceleration–deceleration forces. Although often subtle and overlooked when more dramatic injuries are present, its potential to be progressive and develop into respiratory insufficiency underlines its serious nature.[11]

In our series, there were 63 (10.3%) flail chests. The majority of these injuries occurred in patients with multiple injuries. In patients with flail chests, 53.9% had two or more extrathoracic systems injured; only 14.3% of patients had injuries confined to the chest. We report a mortality rate of 28.6%. There were 39 major pulmonary complications within the group, the most common being prolonged intubation (greater than 1 week), pneumonia, and ARDS. Of these 63 patients, 31 (49%) sustained pulmonary contusions and bilateral pulmonary contusion developed in three patients. In the general group, there were 113 unilateral pulmonary contusions and 21 bilateral contusions or 30%.

Cardiac Contusions

Cardiac contusion from blunt chest trauma occurs frequently, ranging from 16% in autopsy studies[12] to 76% in clinical studies.[13] The clinical presentations of such injuries are extremely variable and are frequently unnoticed in the multitraumatized patient. The spectrum of symptoms and signs ranges from the asymptomatic patient to the patient with severe cardiac compromise. Arrhythmias and conduction defects are the most common complications of cardiac contusions.

The heterogeneity of cardiac contusions is related to the evolving method of diagnosis. The most sensitive method for diagnosis is probably an understanding of the mechanism of injury, awareness of possible associated injuries, and a high index of suspicion. Other methods include admitting and serial electrocardiograms (ECGs), assessment of cardiac isoenzymes, two-dimensional echocardiogram, multiple gated acquisition (MUGA) scan, and evaluation of Swan–Ganz thermodilution cardiac output.[14,15] The more compulsively the diagnosis is pursued, the more frequent is the reported incidence.

The usual clinical course is therefore one of resolution. However, in the acute injury phase, morbidity could be high. A small number of patients with high morbidity will develop a course of chronic arrhythmias or overt cardiac compromise. The incidence of morbidity is probably multifactorial, relating to size and location of contusion, premorbid cardiac status, and associated injuries.

In our series, we identified 33 patients with cardiac contusions. The diagnosis was made using ECG in two, MUGA scan in 11, echocardiogram in four, cardiac isoenzymes in two, thermodilution cardiac output in two, and gross inspection of the heart during thoracotomy in four. Eight patients carried the diagnosis of cardiac contusion without a specific diagnostic test listed. There were four deaths in this group: three patients died during the acute resuscitative phase, presenting with shock, and one (late) died of sepsis. In two patients, significant arrhythmia developed that was controlled medically (one with premature ventricular contractions [PVCs] controlled with lidocaine and one with bradycardia controlled with atropine and a temporary pacer). A persistent right bundle branch block developed in one patient. Although no late follow-up information was available, no patient had persistent symptoms of cardiac compromise on discharge.

Cardiac/Pericardial Injuries

Cardiac lacerations from blunt trauma are usually lethal injuries that are frequently diagnosed postmortem. There are scattered case reports in the literature of survival from this injury; however, the insult to the heart and concomitant associated injuries frequently result in death.[16] Pericardial injuries have also been reported as a cause of morbidity and mortality.[17]

In our series, there were 14 cases of cardiac lacerations and no survivors. Eight of the 14 patients arrived with no vital signs, five patients had severe hypotension (initial blood pressure <60 mmHg), and one patient had stable vital signs initially that rapidly changed to significant hemodynamic instability. Emergency thoracotomies were performed in the admitting area on all patients. The injury pattern to the heart involved all chambers, with four injuries involving the right ventricle, three injuries to the right atrium, two injuries to the left atrium, and one injury to the left ventricle. Four patients had injuries involving a combination of two injured chambers. Seven patients had two or more associated injuries. All patients had tamponade before thoracotomy, and a repair or attempt at primary repair using horizontal pledgetted sutures was done in all cases.

An additional four patients sustained pericardial tears that did not violate the cardiac chambers. Two of the four patients arrived with no vital signs; emergency thoracotomies were unsuccessful. One patient arrived in shock and quickly became asystolic; again, emergency thoracotomy was unsuccessful. The fourth patient arrived with stable vital signs and was taken to the operating room for repair of associated intra-abdominal injuries. A thoracotomy was performed because of ongoing hemothorax. Parenchymal injury to the lung was present, associated with a tear in the pericardium, which

TABLE 3. *Morbidity in 515 Cases of Blunt Trauma*

	N
Atelectasis	38
Pneumonia	35
ARDS	33
Empyema	20
Recurrent pneumothorax or persistent leak	24
Aspiration	9
Miscellaneous*	30

* Lung cyst, lung abscess, arrhythmias, pericarditis, pericardotomy syndrome, sternal dehiscence, pericardial herniation, chylothorax, thoracotomy wound infection, myocardial infarction, paraplegia, aortoesophageal fistula, barotrauma, bleeding.

ARDS = acute respiratory distress syndrome.

was repaired. There was no cardiac injury, and the patient had an unremarkable course.

Great Vessel Injuries

Like injuries to the aorta, an insult to the branches of the aortic arch, thoracic vena cava, or pulmonary hilar vessels connotes a life-threatening injury. A majority of patients with these injuries have severe concomitant injuries and die at the scene or are dead on arrival. A diagnosis of great vessel injury is made by having a high index of suspicion from the mechanism of injury, associated injuries, and physical examination and detection of an abnormal mediastinum by chest x-ray. A suspicion of such an injury mandates an aortic arch arteriogram.

Nine patients presented to the MIEMSS Shock Trauma Center with great vessel injuries other than aortic tears. These included three patients with innominate artery injuries, two patients with subclavian artery avulsions, two patients with axillary artery injury, one patient with injury of the azygous vein, and one patient with an avulsed pulmonary artery and pulmonary vein. There were two deaths and three major complications. One death occurred 48 hours after injury and was secondary to significant preoperative hypotension and low flow state. The second death was late (>4 weeks) and due to sepsis. The complications included empyema, brachial plexus injury, and sternal dehiscence.

Discussion

Blunt thoracic trauma is responsible for one fourth of all traumatic deaths in the United States. In our analysis, we have identified several areas of interest.

The absence of rib fractures or other bony thoracic injuries does not preclude other serious chest injuries. Indeed, 47.4% of the ruptured aortas, 43.5% of the ruptured diaphragms, 50% of the tracheobronchial injuries, and 60.6% of the cardiac contusions presented in the absence of thoracic fractures. Whether this occurs because the energy of acceleration/deceleration forces is not dissipated through the fractures or because a specific type of kinetic force predisposes the patient to soft tissue injury instead of bony injury is unclear. Of importance is that a serious thoracic injury may be present without associated rib or other overt thoracic fractures. To identify these patients, an index of suspicion for blunt thoracic trauma must be maintained based on history, mechanism of injury, and physical examination, despite the absence of fractures.

Within our group of patients with ruptured diaphragms, we identified a high incidence of right-sided diaphragmatic injuries. Although the majority of ruptured diaphragms continued to predominate on the left side, 30% were right sided, a figure much higher than the 5–10% that is often cited. The right-sided lesions are often more subtle in presentation radiographically and can represent a missed injury if an index of suspicion is not raised.[7]

Emergency room thoracotomies continue to be controversial in blunt trauma. All patients in this study who had absent vital signs in the emergency room died despite aggressive resuscitative measures, which included emergency left thoracotomy (39 patients). Emergency thoracotomy might be effective in the treatment of a ruptured cardiac chamber or severe pulmonary parenchymal laceration. However, all patients with these injuries died despite emergency thoracotomy.

The dismal results of our emergency thoracotomies reflect the findings in other studies, which indicate that patients with absent vital signs at the scene, or for greater than 30 minutes after injury, cannot be resuscitated.[18] Nevertheless, because the decision to perform an emergency thoracotomy requires an immediate decision, often with incomplete and inaccurate data concerning the patient, we hesitate from making sweeping recommendations concerning emergency thoracotomies.

Our general philosophy remains that if there is any doubt about a patient's immediate or subsequent clinical status, it is better to err on the side of resuscitation rather than declaring the patient dead on arrival. However, if the patient has no vital signs at the scene or has been without vital signs for 30 minutes, this represents a nonsalvageable patient.

Morbidity

We identified 185 patients (36%) with a morbidity secondary to their chest trauma (Table 3). Atelectasis, confirmed radiographically and significant enough to cause fever and require bronchoscopy or vigorous physical therapy, was the most common complication. Pneumonia, ARDS, and recurrent pneumothoraces were other common complications. An unusual complication of a ruptured thoracic aorta was an aortoesophageal

TABLE 4. *Mortality in 515 Cases of Blunt Chest Trauma*

	No. of Patients	%
Early deaths	64	80
Late deaths	16	20
Total	80	15.5

TABLE 5. *Causes of Late Death Occurring >72 Hours After Injury*

	N
ARDS	8
ARDS/sepsis	3
ARDS/MSOF	2
Fatty embolus	1
Aortoesophageal fistula	1
Other	2

ARDS = acute respiratory distress syndrome.
MSOF = multiple system organ failure.

fistula that presented several months after successful repair and subsequently proved fatal.[9] In general, we believe that early mobilization, aggressive analgesia, vigorous physical and respiratory therapy, and bronchoscopy, if other measures fail, are essential in reducing the majority of pulmonary complications from chest trauma.

Mortality

The mortality rate in this study was 15.5%, representing 80 patients (Table 4). Fifty-nine of these patients arrived with absent vital signs or had cardiac arrest within 1 hour of their arrival. Eight patients died of a primary insult to their central nervous system. There were 16 late thoracic deaths (defined as deaths after 72 hours of hospitalization and primarily related to their thoracic trauma). The causes of death included ARDS, sepsis, heart failure, and multiple organ failure (Table 5).

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Malignant Melanoma

Practical Considerations Concerning Prophylactic Regional Lymph Node Dissection

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Seventy-three patients had 77 prophylactic regional lymph node dissections (PRLND) in addition to wide excision of the primary lesion for clinical Stage I primary malignant melanoma. The preoperative evaluation, surgical procedure, and postoperative follow-up were performed by one surgical oncologist. Seven patients had micrometastatic disease in the regional nodes for a yield of 9.6%. Considering only patients with Clark IV and V melanomas, and Clark III melanomas ≥ 2.00 mm, the yield was 15.6%. The most optimistic, published survival statistics demonstrate a 25% 5-year survival advantage for patients who have PRLND with an incidence of occult nodal disease of 14.3%; thus, even the most optimistic data would predict that only a modest number of patients would actually benefit from surgery. It is difficult to justify PRLND for its therapeutic benefit unless a higher yield of positive-node patients is obtained or the surgical indication is for staging or prognostic information.

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IT REMAINS CONTROVERSIAL whether prophylactic regional lymph node dissection (PRLND) should be considered in patients who have primary malignant melanoma and clinically negative regional lymph nodes. The advocates point out correctly that surgery is the only effective therapy for regional lymph node disease; moreover, in several retrospective studies a survival advantage by as much as 25% has been demonstrated in patients with clinically negative but pathologically positive regional lymph nodes.[1,2] Roses et al, from New York University, demonstrated a statistically significant 5-year cumulative survival rate of 57% for 60 patients with clinically negative, but pathologically positive, lymph nodes compared with a 33% 5-year cumulative survival rate for 35 patients with clinically positive and pathologically positive lymph nodes.[1] Balch et al, from the University of Alabama, reported that patients with intermediate-thickness melanomas (1.5–3.99 mm) had a survival rate at 8 years of 78% when treated by wide excision of the primary melanoma and elective lymph node dissection compared with no survivors with wide excision alone.[2]

The opponents of PRLND point to the randomized, prospective, multi-institutional study by Veronesi et al., of the WHO Melanoma Group, which failed to demonstrate any survival advantage in patients who have prophylactic lymph node dissection.[3] In the WHO study, 267 patients were randomized to excision of the melanoma with immediate lymph node dissection and 286 patients to excision of the primary lesion and regional lymph node dissection at the time of appearance of metastases.

The advocates counter with the argument that the WHO study was flawed in that the percentage of women in the study was too high (81%). This is of concern since the incidence of melanoma is approximately equal between the sexes; thus, in a prospective randomized study, one would predict that the number of men and women accrued would have been about the same. In addition, women overall fare better than men with their disease, even when corrected for stage.[4] Thus, a large, lower-risk group was included in an adjuvant (PRLND) study, making it more difficult to demonstrate small, but statistically significant, differences. Also of concern is that the subgroup of patients with Clark IV melanomas having PRLND did, in fact, have a survival advantage (70.1% *vs.* 58.3% 5-year survival rate) as did the subgroup with intermediate-thickness melanomas (1.6–4.5 mm) (78.5% *vs.* 69.7% 5-year survival rate). Since these differences were not statistically significant, it was concluded that these differences were not real. However, an equally valid conclusion would be that the

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differences were real, but that there were not enough patients in the subgroups (Clark IV subgroup: 178 patients; intermediate-thickness subgroup: 187 patients) to demonstrate statistical validity. Finally, the multi-institutional, international nature of the study (17 institutions, 12 countries) may be considered a flaw since it implies that the preoperative evaluation, the surgical technique, and the postoperative follow-up may have varied considerably.

This report summarizes one surgeon's experience with PRLND for clinical Stage I malignant melanoma. The advantage of this type of analysis is uniformity in pre- and postoperative care and surgical technique.

Methods

All patients referred with clinical stage I malignant melanoma whose histopathologic examination revealed a Clark IV or V lesion or a thick Clark III lesion had PRLND in addition to a wide and deep excision of the primary lesion. With ambiguous lesions, a Tc 99-dextran lymphatic drainage study was performed to delineate the appropriate lymph node group to be resected. The preoperative evaluation, surgical procedure, and postoperative follow-up were performed by one surgical oncologist.

Results

Between September 1980 and June 1986, 73 patients (29 women and 44 men) had 77 PRLNDs for primary malignant melanoma (Table 1). This included 40 axillary dissections, 21 superficial (inguinal) groin dissections, and 16 modified radical neck dissections. There was 100% follow-up. There was no operative mortality. The long-term morbidity consisted of local numbness in all patients regardless of type of lymph node dissection. After superficial groin dissection, some swelling of the lower extremity could be noted in almost all patients if both limbs were carefully measured. In the 21 patients who had superficial groin dissection, four patients have had obvious lymphedema develop, requiring some change in life style. The long-term morbidity after axillary or modified radical neck dissection has been negligible.

The histopathologic findings consisted of 47 Clark III lesions, 26 Clark IV lesions, and one Clark V lesion (Table 2). The Clark level could not be determined in three patients. In the Clark III group, the Breslow thickness ranged from 0.69 mm to 4.9 mm. In the Clark IV group, the Breslow thickness ranged from 0.87 mm to 7.2 mm. The Clark V lesion had a Breslow thickness of 6.5 mm. In two patients, the Breslow depth could not be determined.

In the group of 38 patients who had 40 axillary lymph node dissections, the average number of lymph nodes examined was 25 (median: 24; range: 10–56). There were four positive dissections in four patients. In the group of 21 patients who had 21 superficial groin dissections, there was an average of 18 lymph nodes examined (median: 18; range: 8–30). There were two positive dissections. In the group of 16 patients who had 16 modified radical neck dissections, there was an average of 25 lymph nodes examined (median: 24; range: 10–65). There was one positive dissection. Overall, seven dissections in seven patients were found to contain lymph nodes with micrometastatic disease (Table 3). The per cent yield then was seven positive dissections of 77 dissections (9.1%) or seven positive dissections in 73 patients for a yield of 9.6% (Table 1). In the 66 patients who had negative lymph node dissections, metastatic disease developed in nine patients (13.6%) (Table 4).

TABLE 1. *73 Patients who had 77 Prophylactic Regional Lymph Node Dissections for Clinical Stage I Malignant Melanoma*

	N	No. of Patients*	Lymph Nodes Examined (Avg)	Positive Dissections
Axillary dissection	40	38	25	4
Superficial groin dissection	21	21	18	2
Modified radical neck dissection	16	16	25	1
Total	77	73		7 (9.1%)

* Two patients had bilateral axillary dissection. Two patients had axillary dissection and modified radical neck dissection.

TABLE 2. *Histopathologic Findings in 73 Patients with Primary Malignant Melanoma*

Clark Level	No. of Patients*	Breslow Depth (mm) (Range)
III	43	0.69–4.9
IV	26	0.87–7.2
V	1	6.5

Breslow Thickness (mm)	No. of Patients†	Clark Level		
		III	IV	V
<1.00	12	6	6	0
1.00–1.49	21	15	6	0
1.50–1.99	7	6	1	0
2.00–2.49	14	10	3	0‡
2.50–2.99	3	0	2	0‡
3.00–3.49	5	2	3	0
3.50–3.99	4	2	2	0
>3.99	5	2	2	1

* Three patients with indeterminant Clark level.
† Two patients with indeterminant Breslow depth.
‡ Indeterminant Clark level.

TABLE 3. *Data Concerning Seven Patients with Clinically Negative but Pathologically Positive Lymph Nodes*

Patient	Clark Level	Breslow Depth (mm)	No. of Positive Nodes/Total Nodes	Date of Surgery	Status
1	III	4.9	2/11 (Groin)	9/80	NED
2	IV	5.6	3/17 (Groin)	9/80	Dead (lung)
3	IV	2.5	2/56 (Axilla)	12/80	Dead (lung)
4	III	3.2	1/26 (Neck)	2/81	Dead (brain)
5	III	4.4	1/14 (Axilla) 0/19 (Axilla)	5/82	NED
6	V	6.5	2/26 (Axilla) 0/26 (Neck)	3/83	Dead (lung)
7	III	2.14	1/21 (Axilla)	10/84	In transit metastasis: NED

NED = No evidence of disease.

Discussion

The controversy surrounding prophylactic regional lymph node dissection in patients with clinical Stage I malignant melanoma continues despite the Veronesi study that failed to demonstrate a therapeutic benefit for patients who have prophylactic node dissection.[3] The reasons for this are several-fold. First, the Veronesi study, as noted above, has several flaws that detract from its conclusions. Second, many patients, after considering the risks and benefits of elective lymph node dissection, believe that the possible small benefit from surgery outweighs the risks. In addition, the patient is often interested in the prognostic information obtained from the lymph node dissection since pathologically negative nodes puts the patient in a lower risk category compared with patients with pathologically positive nodes. Also, adjuvant trials often require the patients to have lymph node dissection for accurate staging before the onset of therapy. Thus, the surgical oncologist, when faced with a new patient with clinical Stage I melanoma, must still make a decision regarding PRLND.

From the therapeutic point of view, the only patients that currently benefit from PRLND are those whose nodes are positive and who are free of distant metastatic disease, *i.e.*, the patient classified as N_1M_0 by the TNM classification. Clearly, not all patients with positive nodes benefit from PRLND since many, if not all, are pathologically N_1M_1 at the time of surgery. Thus, if the incidence of occult metastatic disease in the regional nodes is only 15% in patients with clinical Stage I disease, then the actual number of patients being benefited therapeutically is small. In the study of Roses et al., the incidence of positive nodes in clinically negative patients was 14.3%.[1] Even if we assume that the 25% 5-year survival advantage observed by Roses et al. (comparing patients with clinically negative nodes who had PRLND with patients with clinically positive nodes who had therapeutic node dissection) is correct, it becomes evident that only a very small number of patients actually benefit from PRLND. The mathematics, then, even using the most optimistic survival data, make it difficult to justify PRLND for its therapeutic benefit.

However, PRLND could be justified if the yield of patients with positive nodes were higher. This could be accomplished by selecting patients with thicker lesions for lymph node dissection. In our series, by raising the criteria for surgery to Clark IV and V lesions and Clark

TABLE 4. *Nine Patients with Clinically Negative and Pathologically Negative Lymph Nodes who had Recurrence*

Patient	Date of Surgery	Clark Level/Breslow Depth (mm)	LND/No. of Nodes Examined	Site of Recurrence/Status
1	8/81	III/3.62	Axilla/0/17	Retroperitoneum/Dead
2	12/81	—/2.5	Neck/0/12	Lung/Dead
3	12/83	III/1.7	Bilateral Axilla/0/16, 0/19	In transit/NED
4	4/84	IV/138	Neck/0/17	Lung/Dead
5	8/84	IV/3.5	Axilla/0/24	In transit/NED
6	12/84	IV/0.9	Groin/0/14	In transit/NED
7	3/85	III/2.4	Neck/0/44	Opposite neck, lung/AWD
8	11/85	IV/3.5	Axilla/0/34	Local subcutaneous metastasis/NED
9	2/86	IV/—	Neck/0/25	Distant subcutaneous metastasis/NED

LND = Lymph node group dissected.
NED = No evidence of disease.
AWD = Alive with disease.

III lesions ≥ 2.00 mm, the yield of patients with positive nodes would have been increased from 9.6 to 15.6%. This is similar to the incidence of positive nodes observed in the study of Roses et al.[1]; thus, the therapeutic advantage obtained could only be modest at best.

However, a higher yield may also be obtained by more accurate pathologic review. Cochran et al. have shown that S-100 protein staining in addition to standard hematoxylin and eosin (H & E) staining may increase the number of positive nodes by as much as 2–3 fold.[5,6] In one study, sections of 1273 nodes from patients with melanoma were stained in an immunoperoxidase assay using an antiserum to S-100 protein and aminoethyl carbazole as an indicator. By the H & E technique, 128 nodes were seen to contain melanoma; by the anti–S-100 technique, 363 nodes were found to be tumor-positive.[5] In a second study, Cochran et al. found that the likelihood of finding occult micrometastatic melanoma in the regional nodes using the S-100 protein staining technique increased with increasing melanoma thickness.[6] In a group of 72 patients who were pathologically determined as Stage I by H & E staining, using anti–S-100 staining, they found micrometastatic disease in 4% of patients with a Breslow thickness of ≤1.5 mm, in 12% of patients with a Breslow thickness of 1.5–3.0 mm, and in 17% of patients with a Breslow thickness ≥ 3 mm. Inaccurate pathologic staining may explain why approximately 15% of patients with negative nodes have recurrence, *i.e.,* they did in fact, have positive nodes unrecognized by standard H & E staining.

PRLND can also be justified as a means to obtain prognostic information and as an entrance requirement for an adjuvant trial, since accurate staging is important in evaluating adjuvant therapy. However, the minimal therapeutic benefit would have to be clearly explained to the patient if the indication for surgery were for prognostic or staging information.

This report is by a surgical oncologist who believes that the removal of microscopic disease, as opposed to gross nodal disease, must be to the patient's benefit. As a result, all patients referred with Clark IV and V malignant melanomas and thick Clark III malignant melanomas had PRLND in addition to wide excision of the primary lesion. However, given a yield of only 15% in patients with clinically negative regional lymph nodes, the mathematics, even with using the most optimistic survival data, make it difficult to justify PRLND for its therapeutic benefit. Pathologic evaluation with anti–S-100 staining may increase this yield sufficiently to justify PRLND in the future.

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A Comparison Between 25% Albumin and 6% Hydroxyethyl Starch Solutions on Lung Water Accumulation During and Immediately After Cardiopulmonary Bypass

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Six per cent hydroxyethyl starch was compared prospectively with 25% albumin as the oncotic component of cardiopulmonary pump prime solutions. Oncotic pressure of the pump prime solution was measured, and serum oncotic pressure (OP) values were recorded at designated times during the perioperative period. Changes in these values were compared with alterations in extravascular lung water (EVLW), the serum oncotic pressure–pulmonary artery occluded pressure gradient and the alveolar–arterial difference in oxygen tension [D(A-a)O_2] before and immediately after bypass and in the surgical intensive care unit after operation. A significant increase in EVLW was associated with a decrease in serum OP and an increase in D(A-a)O_2 immediately after bypass. However, EVLW values had returned to baseline by time of determination in the surgical intensive care unit. Cost savings may be realized by the use of hydroxyethyl starch in this setting if average wholesale price data are representative of costs throughout the country.

POSTOPERATIVE AND POSTRESUSCITATION pulmonary dysfunction have been linked to increases in extravascular lung water (EVLW) and associated changes in the gradient between serum colloid oncotic pressure (COP) and the pulmonary artery occluded pressure (PAOP).[1] Although no differences in pulmonary oxygenation, myocardial behavior, and glomerular filtration rate have been reported after cardiopulmonary bypass (CPB) procedures in which colloid and noncolloid pump primes were compared,[2] a recent study suggests that colloid is preferable to crystalloid in pump prime solutions.[3] Several studies have indicated that 6% hydroxyethyl starch (Hes) (Hespan,® American Critical Care, Division of American Hospital Supply Corporation, McGaw Park, IL) is an acceptable substitute for 5% albumin in pump prime solutions, and after CPB causes no change in chest tube drainage, fluid balance, or blood product use although transient decreases in platelet count were noted.[3–8] Interest in decreasing the cost of medical care has made the question of alternative forms of treatment germane, and the purpose of this study was to determine whether or not the use of Hes as a substitute for 5% albumin in cardiopulmonary pump prime solutions altered EVLW accumulation and pulmonary function in the immediate post bypass period and early postoperative recovery period.

Methods

After obtaining institutional approval and informed patient consent, two groups of 10 patients were prospectively studied. The pump prime was formulated in identical fashion for the two groups (Table 1) with the single difference being the addition of 150 mL of 5% albumin in one group *versus* the addition of 500 mL of 6% Hes in the second group. Patients were randomized to receive either an Hes-containing prime or the standard albumin solution. No changes in preoperative patient preparation or anesthetic management were made. Patients continued receiving cardiac medications up to surgery and all were premedicated with 10 mg of oral diazepam. No attempt to blind the study was made. Consecutive consenting patients for coronary artery bypass grafting (CABG) were used because the study called for a test of fluid shifts during CPB, and patient selection was not believed to play a major role in this process. CABG procedures without valve replacement were selected to standardize surgical manipulation and cross-clamp and total bypass times.

Each patient served as his own control. Change in pulmonary function was measured by the alveolar–arterial difference in oxygen tension (D(A-a)O_2), and it was

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compared with changes in EVLW and the COP–PAOP gradient determined before and after CPB and in the surgical intensive care unit (SICU). Additionally, changes in EVLW and serum oncotic pressure (OP) were compared with a control value after anesthetic induction but before CPB, and determinations made immediately on separation from the bypass circuit, before transfer from the operating room to the SICU, during the evening after surgery after stabilization in the SICU and on postoperative day 1. Volume infusion before obtaining the first and subsequent EVLW measurements was minimized and similar in all cases. OP measurements were performed on the pump prime solution. All OP determinations were performed in duplicate on a Wescor Model 4100 colloid osmometer (Warren E. Collier, Inc., Boston, MA), which uses a specially modified Statham P231D transducer (Statham Instruments, Oxnard, CA) with built-in negative offset. Lung water determinations were performed in duplicate using a thermal/dye double indicator technique that has been previously described (American Edwards Model 9310 lung water computer, American Edwards Laboratories, Santa Ana, CA).[9] The technique requires placement of a femoral arterial, thermistor-tipped catheter that is connected to an infusion-withdrawal pump and to the lung water computer. This catheter was placed by the operating surgeon after induction of anesthesia and full patient preparation to avoid chances of contamination in the surgical field. During CPB the lungs were inflated with a continuous low flow of oxygen at 1–2 cm H_2O PEEP and the left ventricle was vented. All patients received continuous infusions of sodium nitroprusside and nitroglycerin after CPB to maintain a mean systemic pressure of 90 mmHg or less. Statistical analysis used analysis of variance with repeated measures. A value of $p < 0.05$ was considered significant.

Statistical Results

Extravascular Lung Water Changes (Tables 2 and 3)

Within each group, significant changes occurred in EVLW (Table 2) and OP (Table 3) between pre-CPB and post-CPB values. However, there were no significant differences between groups. Control values were reached for all parameters by the time of patient entry into the SICU. Although a trend relating increasing EVLW to decreasing OP was noted, it did not achieve significance.

Changes in $D(A\text{-}a)O_2$ Values (Table 4)

No significant differences existed between the albumin and Hes groups. A highly significant difference ($p < 0.0005$) was noted between control and $D(A\text{-}a)O_2$ on postoperative day 1 in both groups, and this was associated with an increase in OP–PAOP gradient and a decrease in EVLW to control value at this time. In the Hes group a significant difference was seen between control and post-CPB OP–PAOP gradient; however, no difference was noted in the albumin group or between groups for this parameter.

TABLE 1. *Pump Prime Composition*

Normosol-R pH 7.4	2500 mL	
Albumin 25% (3 bottles)	150 mL	$225.00
Mannitol 25%	125 g	
Potassium chloride	10 mEq	
Tham (1.8 g)	15 mEq	
Heparin (1000)	20 mg	
Hespan® (500 mL)		$54.38*

* From average wholesale price in Cardinale VA, ed. The Red Book. Oradell: Medical Economics Company, Inc., 1986.

Discussion

Although accumulation of lung water after CPB has been reported, some authors have failed to demonstrate any increase.[4] Previous discussions have speculated on various causes of lung water accumulation after CPB, and most include discussions of the balance between the microvascular hydrostatic pressure and the plasma colloid oncotic pressure.[4,10] Additionally, the use of Hes as an effective volume expander in CPB[3,6,7] and in hypovolemic and hemorrhagic shock[11-15] is well demonstrated. Although other factors have been implicated in accumulation of lung water after CPB (pulmonary capillary leak,[16] complement mediated leukostasis,[17] and changes in the pulmonary circulation secondary to high generated pressures or atelectasis during bypass[4]), no study has documented the immediate changes in lung water seen at the termination of CPB and compared with a pre-pump control value. No patient had severe postoperative cardiac dysfunction develop. However, the experimental design was such that changes in EVLW as a result of CPB could be isolated from later cardiac dysfunction and the known changes in COP occurring because of interstitial fluid shifts and the release of preformed albumin into the circulation.[18]

From the results in Tables 1–4, the following conclusions are drawn: (1) The oncotic pressure is similar with Hes and albumin primes. (2) CPB decreases COP and increases EVLW. (3) Early postoperative increases in

TABLE 2. *EVLW (mL/kg) in Both Patient Groups*

	Before CPB	After CPB	ICU	POD
Hes	7.56 ± 1.3	9.6 ± 1.01*	8.62 ± 0.84	7.0 ± 0.97
Albumin	8.41 ± 1.08	10.69 ± 1.96*	8.57 ± 1.4	7.64 ± 0.25

* Significant at $p < 0.05$ compared with pre-pump values.

TABLE 3. *OP (mmHg) in Both Patient Groups and in Pump Prime Solutions*

	Pump Prime	Before CPB	CPB	After CPB	ICU	POD
Hes	2.76 ± 0.6	17.16 ± 1.67	10.36 ± 0.86*	11.92 ± 0.94	14.54 ± 1.36	17.42 ± 0.34
Albumin	1.82 ± 0.77	15.7 ± 1.23	9.94 ± 0.9*	11.06 ± 0.5	14.44 ± 1.07	17.58 ± 0.52

* Significant at $p < 0.05$ compared with pre-pump values.

TABLE 4. *$D(A\text{-}a)O_2$, OP–PAOP Gradient and EVLW in Both Patient Groups*

	Before CPB	After CPB	SICU	POD 1
Hes				
$D(A\text{-}a)O_2$ (mmHg)	325.4 ± 36.98	391.6 ± 18.51	204.4 ± 13.95	120.8 ± 20.17†
OP–PAOP (mmHg)	6.76 ± 1.55	−1.8 ± 1.91	2.14 ± 0.99*	6.02 ± 0.75
EVLW (mL/kg)	7.56 ± 1.31	9.61 ± 1.02	8.86 ± 0.84	7.0 ± 0.97
Albumin				
$D(A\text{-}a)O_2$ (mmHg)	308.4 ± 50.2	402.6 ± 12.75	207.2 ± 18.69	116.4 ± 13.97†
OP–PAOP (mmHg)	5.1 ± 1.23	−2.74 ± 1.03	2.84 ± 1.11	5.18 ± 1.32
EVLW (mL/kg)	8.41 ± 1.19	11.09 ± 2.15	8.57 ± 1.4	7.64 ± 0.25

* $p < 0.05$ compared with pre-CPB values.

† $p < 0.005$ compared with pre-CPB values.

$D(A\text{-}a)O_2$ are associated with an increase in EVLW and decrease in the COP–PAOP gradient. These changes reversed over time and had returned to control values by completion of the study on postoperative day 1. (4) No significant difference can be shown between Hes or albumin as a pump prime colloid solution. (5) Additionally, it is likely that significant cost savings may be realized by adopting Hes as a routine pump prime solution instead of albumin.

Unlike Byrick et al.,[10] we noted the maximal increase in EVLW to be associated with termination of CPB, therefore suggesting that bypass itself is causative. Additionally, in agreement with Gallagher et al.[4] and in contrast with Byrick et al.,[10] lung water decreased from the values obtained after CPB and returned to control values on postoperative day 1. This, indeed, may reflect a greater COP in the postoperative period, and it is likely that in the postoperative period, hydrostatic-oncotic pressure differences may be primarily responsible for regulating fluid flux across the lungs.

Additionally, the results in this study differ slightly from those of Gallagher et al.[4] in that a significant increase in EVLW was noted after CPB. However, this increase was transient and ceased to be statistically significant by the time determinations were performed in the postoperative SICU. Therefore, when time courses are similarly compared, the results of these two experiments are in accord, and both differ from the reported levels of Byrick et al.[10]

Cost savings per pump prime are approximately $170.00 by substituting one 500-mL bottle of Hes for 150 mL of 5% albumin solution.

Conclusions

This study confirms previous reports that postoperative accumulation of lung water is not significant if measured in the postoperative intensive care unit. However, transient but statistically significant increases were shown immediately after CPB. $D(A\text{-}a)O_2$ values increased in both groups after CPB, but this was not significant statistically nor clinically, although pre-CPB values were high and may represent 100% inspired oxygen-induced atelectasis and intrapulmonary shunt. No difference was shown between the choice of 25% albumin or 6% Hes solutions in the pump prime with respect to oncotic pressure of the prime itself or to the changes in EVLW measured during CPB. Mild changes in pulmonary function as reflected by an increase in $D(A\text{-}a)O_2$ were associated with a decrease in COP and increase in the COP–hydrostatic pressure gradient, suggesting that these are the major determinants of lung water change. Substantial financial savings may be realized by the substitution of albumin with Hes in cardiac pump prime solutions without altering operative outcome.

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Regulation of Lipolysis in Severely Burned Children

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In this study, the rates of lipid mobilization and of lipolysis have been quantified in severely burned children. In all 12 patients studied, the basal rates were determined. In seven patients, the lipolytic responsiveness to an infusion of epinephrine (0.015 μg/kg/min) was tested, and in the other five patients, the response to beta-adrenergic blockade (propranolol, 1 mg/kg) was tested. The rate of appearance (Ra) of free fatty acids (FFA) was quantified by means of the infusion of 1-^{13}C-palmitate to determine the rate of lipid mobilization, and Ra glycerol was determined using d_5-glycerol to assess the rate of lipolysis more directly. In five patients, body composition was determined after recovery by means of $H_2{}^{18}O$ dilution. The basal rate of lipolysis was higher than normal in the burned children. In four of the seven patients infused with epinephrine, there was a pronounced increase in Ra glycerol. In all patients given beta-blockade, Ra glycerol decreased greatly. Changes in Ra FFA corresponded with the changes in Ra glycerol in each case. Total body fat was very low (approximately 2% body weight), reflecting the surgical removal of fat in the process of burn wound excision. From these data it is concluded that lipolytic responsiveness to catecholamines in severely burned children is variable, but not absent, despite chronically elevated levels of catecholamines. The total extent of lipolysis may be limited by the available fat mass in children treated with fascial excision. In such patients, the limitation in the ability to mobilize an adequate amount of FFA to fully meet energy requirements provides an important rationale for the clinical practice of providing nutritional support in hourly boluses, as opposed to infrequent meals, since any period of even a few hours in which nutrients are not being absorbed will result in an energy substrate deficiency and consequent increase in amino acid oxidation.

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THE ABILITY TO MOBILIZE endogenous fat is essential for energy balance because free fatty acids (FFA) normally serve as the major energy source in the postabsorptive state. Fatty acid kinetics are, therefore, important in any pathologic state. The ability to mobilize endogenous FFA in severe burn injury is particularly important because of the increased rate of energy expenditure.[1]

Previous studies in animals[2] and human patients[3,4] have shown that basal FFA flux is elevated after burn or other forms of traumatic injury. Since catecholamines are potent stimulators of lipolysis,[5] and since catecholamines are chronically elevated in severely burned patients,[6] one would expect that the catecholamines play an important role in the stimulation of lipolysis in burned patients. However, the only previous study in which FFA kinetics were determined in burned patients raised doubt as to the importance of the catecholamines in stimulating lipolysis, since these authors failed to identify any relationship between FFA flux and the plasma catecholamine concentrations.[3] However, there are reasons to further explore the role of the catecholamines in stimulating lipolysis in burned patients. First, FFA flux is a reflection not only of lipolysis, but also of the rate of re-esterification of fatty acids within the adipocyte before entering the plasma. The rate of release of glycerol is a better reflection of lipolysis than FFA flux. Glycerol appears in the plasma only as a result of lipolysis,[7] and glycerol cannot be re-esterified within the adipocyte.[8] Thus, all free glycerol resulting from lipolysis appears in plasma. Secondly, a quantitative relationship between plasma catecholamine concentration and lipolysis might not be expected throughout the en-

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tire range of plasma catecholamine concentration encountered in burn patients. In some patients, catecholamine concentrations are so high that they probably greatly exceed the value of maximal biologic effectiveness. Also, the sensitivity to catecholamines may be altered, such that a level of plasma epinephrine that is below the threshold for lipolytic stimulation in normal individuals[9] may be effective in stimulating lipolysis in burned patients.

In this study, we have used two approaches to assess the effectiveness of catecholamines in stimulating lipolysis after severe burn injury: (1) we determined the lipolytic responsiveness to an infusion of epinephrine, and (2) we determined the response of lipolysis to beta-adrenergic blockade. Glycerol flux, as determined with the stable isotopic tracer d_5-glycerol (Cambridge Isotope Laboratory, Woburn, MA), has been used as the indicator of the rate of lipolysis. The rate of flux of palmitate, as a representative FFA, was determined simultaneously with 1-^{13}C-palmitate (Tracer Technology, Newton, MA).

Methods

Patients

The subjects were 12 severely burned children admitted to the Shriners Burns Institute in Galveston. In each case, the purpose of the study and the associated risks were explained in detail to the parents and a patient advocate as part of obtaining informed consent. The study was approved by the Institutional Review Board of The University of Texas Medical Branch in Galveston.

All patients were admitted to the hospital shortly after injury, and after fluid resuscitation were treated with aggressive excisional therapy. Their clinical characteristics are summarized in Table 1. The type of surgical excision used (fascial or tangential) was determined by the judgment of the surgeon. Fascial excision involves removal of the burn wound and everything beneath it (fat) to the level of fascia. Tangential excision, on the other hand, leaves the fat fairly much intact. Each child was maintained in a temperature-controlled room that was adjusted to help maintain the expected body temperature. There was no change in room temperature throughout the study protocol. All studies were performed at least 2 days after the most recent visit to the operating room. The patients were given an average of 108 ± 14.7 kcal/kg/day, with approximately 50% as carbohydrate. Protein intake averaged 3.8 ± 0.56 g/kg/day. This mixture was administered hourly by tube feeding. The tube feedings were terminated 9 hours before the collection of the first samples used for analysis.

TABLE 1. *Patients (N = 12)*

	Age	% TBSA* Burned	Days After Burn	Resting Energy Expenditure cal/kg/min	Resting Energy Expenditure % Predicted†
Mean	8 ± 1.0	77 ± 3.6	19 ± 3.6	36.3 ± 2.6	134 ± 5.0
Range	4–15	60–95	9–48	25–56	116–158

* Total body surface area burned.
† Predicted by the Harris Benedict equation.

All children had a venous and arterial catheter present for clinical purposes. For the purposes of the study, the venous catheter was used for isotope infusion, and the arterial catheter was used for blood withdrawal. After a baseline blood sample, a constant infusion of 1-^{13}C-palmitate and d_5-glycerol was started and maintained for 120 minutes. The palmitate was bound to albumin[10] (Cutter Albumin, Emeryville, CA), and the glycerol was added directly to the albumin–palmitate mixture. The isotopes were infused by means of a calibrated Harvard Syringe Pump (Harvard Apparatus Co., Inc., Natick, MA). The palmitate was infused at approximately 0.04 μmol/kg/min and the glycerol was infused at approximately 0.11 μmol/kg/min, with a prime of 1.6 μmol/kg. The exact infusion rates were determined for each patient by measurement of the concentration of the infusion mixture. The patients were kept supine and as undisturbed as possible throughout the entire isotope infusion.

Samples were taken at 5-minute intervals starting after 30 minutes of isotope infusion. The five samples taken between 30 and 55 minutes were used to determine basal kinetics and concentrations. In seven patients, a constant infusion of epinephrine was started at 55 minutes, at the rate of 0.015 μg/kg/min, through the venous catheter. The epinephrine was constituted in a solution containing ascorbic acid (50 mg) to prevent oxidation. Samples were drawn at 10-minute intervals throughout the 60 minutes of epinephrine infusion.

In five recovered patients, total body water was determined using $H_2{}^{18}O$ for the purpose of calculating the total body fat. A urine sample was obtained, then $H_2{}^{18}O$ (10.45 APE) (Prochem, Summit, NJ) was given orally. The $H_2{}^{18}O$ was administered at a dose estimated to produce an increase of approximately 50 parts per thousand $H_2{}^{18}O$ concentration. All urine produced between 0 and 4 hours after isotope administration was discarded. The first collection after 4 hours was used for the determination of isotopic enrichment, compared with the value obtained before the isotope administration.

In the other five patients, the basal period (isotopes only) lasted 90 minutes; without interruption of the isotope infusion, an infusion of propranolol (Inderal®) then was started. A total of 1 mg/kg, comparable to the dose previously used by Wilmore et al. in burned patients,[6] was given over approximately 10 minutes. Heart rate never decreased below 100 beats/min during the propranolol infusion. Samples were taken at intervals over the next 90 minutes.

Analysis of Samples

The samples for catecholamine analysis were collected in iced tubes containing ethyleneglycol-bis-(beta-aminoethyl ether) N, N^1-tetra-acetic acid (EGTA, 1 mg/mL blood) and reduced glutathione (2 mg/mL blood) and were centrifuged immediately at 4 C. The plasma was separated and stored at −70 C until analysis. Plasma norepinephrine and epinephrine concentrations were determined by a radioenzymatic assay using catechol-o-methyl transferase to label catecholamine-containing compounds with tritium labeled S-adenosyl methionine.[11] Plasma levels of insulin and cortisol were determined by radioimmunoassay using kits from Micromedic (Cambridge, MA). Plasma for glucagon analysis was placed in tubes containing EDTA and Trasylol, for later radioimmunoassay.[12] Plasma glucose concentration was measured on an auto-analyzer (Beckman Instruments Co., Fullerton, CA).

Blood for analysis of palmitate and glycerol enrichment was collected in heparinized tubes and placed immediately in a 4 C ice bath, which prevents the *in vitro* hydrolysis of endogenous triglycerides by lipoprotein lipase.[13] The plasma was promptly separated by centrifugation and frozen until the time of analysis. The samples were processed for quantitative gas chromatography as described by McDonald-Gibson and Young.[14] Heptadecanoic acid (0.05 mg/mL plasma) was added as an internal standard for subsequent measurement of FFA concentration. After conversion to the methyl ester, 1-^{13}C-palmitic acid enrichment was determined by gas chromatography mass spectrometry (GCMS) as described previously[10] using a Hewlett-Packard 5985 GCMS system (Hewlett-Packard, Palo Alto, CA). Ions at mass-to-charge ratios (m/e) of 270.2 and 271.2, representing the molecular ions of unlabeled and 1-^{13}C-palmitic acid methyl esters, respectively, were selectively monitored at 0.1-second intervals and their corresponding peaks integrated. Palmitic acid and total FFA concentrations were quantitated separately on a Hewlett-Packard gas chromatograph.

The blood for glycerol determination was collected in the same manner as that for palmitate. 2-^{13}C-glycerol was added as an internal standard to each sample, except for the background sample. Plasma proteins were then precipitated with $Ba(OH)_2$ and $ZnSO_4$ and the resultant supernatant was passed through anion (Dowex AGI-X8) and cation (Dowex AG-50W-X8) exchange columns. The trimethylsilyl derivative was formed and isotopic enrichment determined by GCMS using electron-impact ionization.[15] Ions were selectively monitored at m/e 205, 206, and 208 to quantify the isotopic enrichment in the plasma resulting from the d_5-glycerol infusion (m/e 208), and to quantify the enrichment that resulted from adding 2-^{13}C-glycerol *in vitro* for the purpose of determining concentration.

^{18}O enrichment was analyzed on CO_2 gas equilibrated with the water in a nonsiliconized, evacuated vacutainer, using a triple-inlet, triple-collector, 6-inch isotope ratio mass spectrometer (Nuclide Corp., State College, PA). Ions at m/e 44, 45, and 46 were each directly collected and monitored.

Calculations

The rates of appearance of palmitate (Ra palmitate) and glycerol (Ra glycerol) were calculated using the Steele equation.[16] In the basal period, when only isotope was infused, a physiologic and isotopic steady state existed, meaning that neither concentration nor enrichment was changing over time. Therefore, the steady-state form of the Steele equation was used.[15] Since palmitate is believed to be typical of other long-chain fatty acids,[17,18] the relationship between flux and concentration of the other fatty acids in plasma was assumed to be the same as for palmitate. Therefore, total FFA flux was calculated by dividing the rate of appearance of palmitate (Ra palmitate) by the fraction of [palmitate]/[total FFA], as determined by gas chromatography.

After the administration of epinephrine or propranolol, the steady state was disturbed. In this case, the non-steady-state form of the Steele equation was used.[16] For palmitate, V (the "effective" volume of distribution) was assumed to be 40 mL/kg, and for glycerol, V was assumed to be 200 mL/kg.

In the rapidly changing non-steady state, the Steele equation often yields unreliable values when raw data are used, because implausible gradients occur in the enrichment/time curve due to random error. Therefore, curve fitting is often necessary to smooth the data. In this experiment, enrichment and concentration data were smoothed by the method of spline fitting, which involves the use of smoothly joined polynomial function segments as a description of experimental data.[19] It is well suited for the data generated in this experiment because the curve-fit data represent the actual data well on small intervals, the values of the fitted curve are little affected by data points that are horizontally distant, and it provides a good overall (least-square) fit.

Once the spline fitting was accomplished, curve-fit data points were taken every 5 minutes throughout the epinephrine or propranolol infusion for the purpose of calculating the Ra. To quantify the magnitude of the response to epinephrine infusion, the area under the Ra *versus* time curve between T = 55 and T = 120 minutes was then calculated according to the trapezoid rule, and the basal value (before epinephrine infusion) was subtracted from the total area.

The estimation of body fat was determined from the calculation of total body water (TBW) as follows[20]:

$$\text{BW (kg)} = \frac{D}{MW} \times \frac{APE}{100} \times 18.02 \times \frac{f}{R_{std} \times \Delta\delta^{18}O}$$

where D is the dose of $H_2{}^{18}O$ (g), MW is the molecular weight of the $H_2{}^{18}O$, APE is the atom percent ^{18}O enrichment of the $H_2{}^{18}O$, f is the ^{18}O fractionation between CO_2 and H_2O (1.0407), $^{R}{}_{std}$ is the ratio of $^{18}O/^{16}O$ in the standard (0.002004) and $\Delta\delta^{18}O$ is the difference between the ^{18}O enrichment in the sample before and 4 hours after isotope administration, compared with our lab CO_2 standard.

and lean body mass (kg) = TBW/0.72

and body fat (kg) = body weight − lean body mass

Statistical Analysis

The experimental design enabled the use of each patient as their own control, in that the value after epinephrine or propranolol infusion was compared statistically with the value in the same patient before the infusion. The resolution of the central questions addressed in this study, *i.e.*, what are the responses to epinephrine or propranolol infusion in burned children? did not require "control" data from unburned children. In some cases, however, we present normal values (determined in our laboratory by the same methods in normal volunteers) as a frame of reference. However, since these normal values were all obtained in adults, they do not serve as adequate "control" values for burned children. Analysis of the responses after infusion with the basal value was performed with either the Student's t-test for paired samples or analysis of variance and Dunnett's t-test.

Results

Epinephrine Infusion (N = 7)

The basal epinephrine concentrations varied widely (range: 72–653 pg/mL), yet the epinephrine infusion caused a relatively consistent incremental increase in epinephrine concentration (Table 2). The average increase was 270 ± 46 (SEM) pg/mL, with a range from 156 to 453 pg/mL. This incremental increase in epinephrine did not result in significant changes in plasma norepinephrine, insulin, or glucagon, all of which were higher than would have been anticipated for normal children.

TABLE 2. *Effect of Epinephrine Infusion on Hormone Concentrations**

Hormone	Basal	Epinephrine Infusion
Epinephrine (pg/mL)	298 ± 87	583 ± 120
Norepinephrine (pg/mL)	1274 ± 420	1171 ± 501
Insulin (μU/mL)	17.2 ± 2.2	14.2 ± 1.3
Glucagon (pg/mL)	310 ± 50	299 ± 49
Cortisol (μg/dL)	37.4 ± 4.5	—

* N = 7, values mean ± SEM.

The rate of epinephrine infusion used (0.015 μg/kg/min) was insufficient to cause significant changes in resting energy expenditure, nitrogen excretion, substrate oxidation (determined by indirect calorimetry), or plasma glucose concentration. Nonetheless, in four of seven patients, the epinephrine infusion caused a pronounced stimulation of lipolysis, as reflected by the rate of appearance of glycerol (Ra glycerol) (Fig. 1). The other three patients, however, did not have any significant lipolytic response to the epinephrine infusion (Fig. 1). The total lipolytic response of each patient for the 60 minutes of epinephrine infusion is shown in Figure 2, as compared with the normal response for adults. Although the response in controls may differ quantitatively in children and adults, the normal value is presented to amplify the dichotomy of response of the burned children. Three of the children apparently had

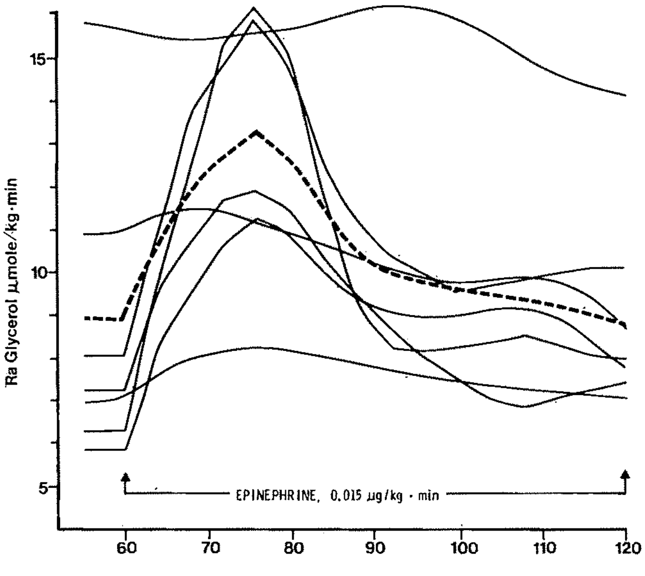

FIG. 1. Rate of appearance of glycerol (Ra glycerol) in seven severely burned children during the infusion of epinephrine. The dotted line represents the mean value and the solid lines represent the individual responses.

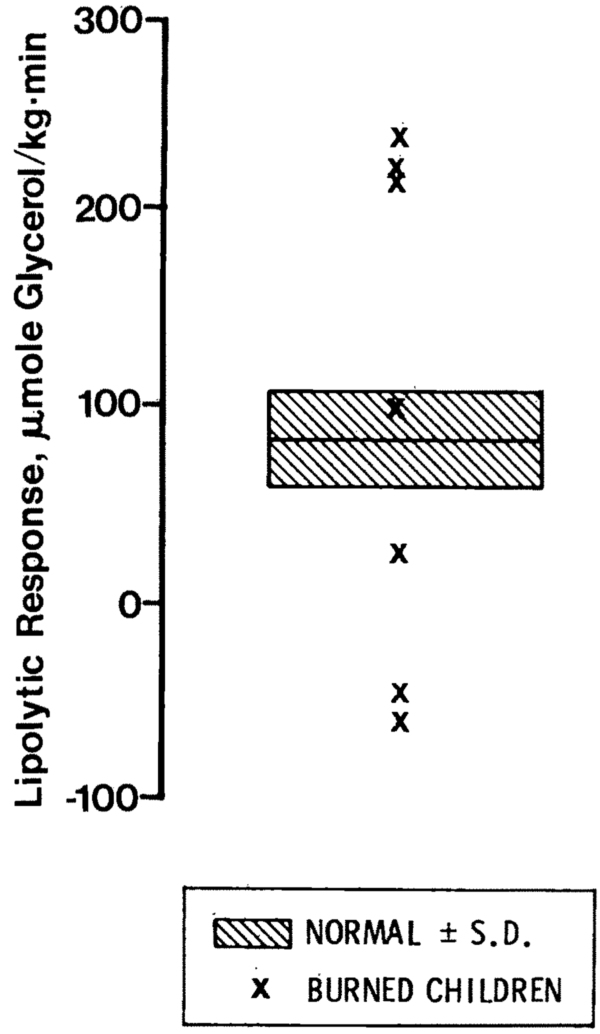

FIG. 2. Total lipolytic response (Ra glycerol *vs.* time) over the 60 minutes of epinephrine infusion. The basal value was subtracted from the epinephrine infusion value. The shaded area represents the mean response, ±SD, of normal adult volunteers (from reference 22).

increased sensitivity to epinephrine, and three were well below the normal level of responsiveness.

Data were evaluated to ascertain a possible explanation for the fact that only some of the patients responded to the epinephrine infusion, despite the consistent elevation in the basal rate of lipolysis in all patients. No consistent difference was found between "responders" and "nonresponders" in the concentration of catecholamines, the basal rate of lipolysis, the percentage of burn, the day after burn, or any other clinical factor measured. The only identifiable variable that may separate the two groups was the extent of fascial, as opposed to tangential, excision in the nonresponders. Those with greater fascial excisions (greater percentage of body surface) had no lipolytic response (Table 3). The estimates of body composition derived from the total body water measurements substantiated that the nonresponders had only a small amount of body fat, as all three such patients had less than 2.5% body fat (compared with the normal value of 15% in age-matched controls, using the same methodology[21]). Although the calculation of exact mass of body fat may be inaccurate with such small amounts of fat, the value of the burned children was clearly far below normal.

The rate of appearance of FFA and plasma FFA concentrations followed the Ra glycerol and glycerol concentrations. The basal values of Ra FFA and FFA concentrations were 14.1 ± 2.1 μmol/kg/min and 0.48 μmol/mL, respectively. The responders reached a peak value of Ra FFA between 22 and 34 μmol/kg/min, and those that did not have an increase in Ra glycerol also did not have an increase in Ra FFA.

TABLE 3. *Effect of Fascial Excision on Lipolytic Responsiveness*

	Lipolytic Response (μmol glycerol/kg h)	% TBSA Fascially Excised
Responders, N = 3	219 ± 14	9 ± 9
Nonresponders, N = 3	−23 ± 27	49 ± 14
Normal values*	86 ± 24	—

* Normal values from reference 22.

TABLE 4. *Effect of Beta-blockade on Hormone Concentrations**

Hormone	Basal	Blockade
Epinephrine (pg/mL)	455 ± 120	—
Norepinephrine (pg/mL)	1843 ± 380	—
Insulin (μU/mL)	22 ± 5	16 ± 3
Glucagon (pg/mL)	330 ± 48	403 ± 52
Cortisol (μg/dL)	26.5 ± 4.5	28.1 ± 5.1

* N = 5, Values are mean ± SEM.

Beta-blockade

The basal hormone concentrations of the patients included in this protocol (Table 4) were comparable to those infused with epinephrine (Table 2), as was their general clinical condition. Infusion of propranolol had no obvious clinical effect, heart rate decreased approximately 15 beats/min, but remained above 100 beats/min in all cases, and no significant change in blood pressure was observed. Subjectively, the patients appeared calmer after the propranolol infusion.

Beta-blockade caused a significant fall in the plasma insulin concentration, but no change in either glucagon or cortisol concentration (Table 4). Nitrogen excretion was not significantly altered by beta-blockade. Although resting energy expenditure fell modestly, this decrease also was not statistically significant (Table 5). Plasma glucose decreased slightly (from 101 ± 9 mg/dL to 93 ± 10 mg/dL) but this also was not statistically significant.

There was a wide range in the basal rate of lipolysis (Ra glycerol ranged from 5.2 to 14.2 μmol/kg/min). Nonetheless, beta-blockade caused a prompt reduction in Ra glycerol in all cases, and this value remained depressed throughout the next 90 minutes (Fig. 3). The plasma concentration of glycerol fell correspondingly. Ra FFA also fell promptly after beta-blockade, from a mean basal value of 13.3 ± 3.1 μmol/kg/min to a low of 7.44 ± 2.33 μmol/kg/min at 40 minutes after propranolol. In all cases after beta-blockade, the potential energy available in the form of plasma FFA was reduced much more than was the overall rate of energy expenditure. All values for Ra glycerol and Ra palmitate after propranolol were statistically significantly lower than the basal values.

Discussion

In this experiment we tested the lipolytic response in burned children to the infusion of epinephrine at a rate sufficient to consistently stimulate lipolysis in normal volunteers.[22] Since lipolysis was stimulated in only four of the seven patients tested, we might conclude that some burn patients become desensitized to the lipolytic action of catecholamines. Such a desensitization response might be expected, since the chronic elevation of epinephrine normally causes a down-regulation of receptors,[5,23] and all of our patients had high levels of epinephrine (presumably for several days).[6] Furthermore, the importance of epinephrine as a lipolytic stimulant in burned patients was questioned by Galster et al.,[3] who failed to find a relationship between the plasma epinephrine concentration and the rate of palmitate flux in burned patients. Alternatively, it is possible that all patients retain responsiveness to the catecholamines, but in some patients the maximum rate of lipolysis was achieved at rest without added infusion of epinephrine.

The principal support for the conclusion that all patients retain responsiveness to catecholamines is the consistent and pronounced decrease in lipolysis observed when adrenergic blockade was given. The decrease in lipolysis was especially impressive, since we probably did not achieve complete blockade despite the large dose of propranolol used (1 mg/kg). In all cases, heart rate remained above 100 beats/min, evidence that some adrenergic stimulation was persisting. Furthermore, blockade caused insulin concentration to fall (Table 4), and a decrease in insulin concentration, by itself, would lead to an increase (rather than decrease) in lipolysis.[7] Thus, the basal adrenergic activity plays an important role in stimulating lipolysis in burn patients.

TABLE 5. *Effect of Beta-blockade on Energy Expenditure**

	$\dot{V}O_2$	$\dot{V}CO_2$	Resting Energy Expenditure	
	(μmol/kg/min)		cal/kg/min	% Predicted
Basal	400 ± 38	318 ± 34	42 ± 4.0	145 ± 26.5
Beta-blockade	340 ± 67	269 ± 58	36 ± 3.3	124 ± 34.1

* N = 5, Values are mean ± SEM.

The fact that epinephrine retains its effectiveness as a stimulator of lipolysis in burn patients, despite the chronic elevation in epinephrine levels, is consistent with the findings of a previous study done in rats. Aprille et al.[24] found that adenylate cyclase from adipose tissue of burned rats retained responsiveness to isoproterenol when assessed *in vitro*. In contrast, adenylate cyclase did become desensitized after isoproterenol injection in unburned rats.[24] The authors proposed that chronic elevations of catecholamines evoke regulatory mechanisms in target cells to circumvent the desensitization that would otherwise occur as a result of acute exposures to catecholamines. It seems this same mechanism is operative in human burn patients as well.

The conclusion that burn patients retain lipolytic sensitivity to catecholamines, however, does not explain the failure of some patients to respond to epinephrine infusion. Although the basal Ra glycerol of the burned pa-

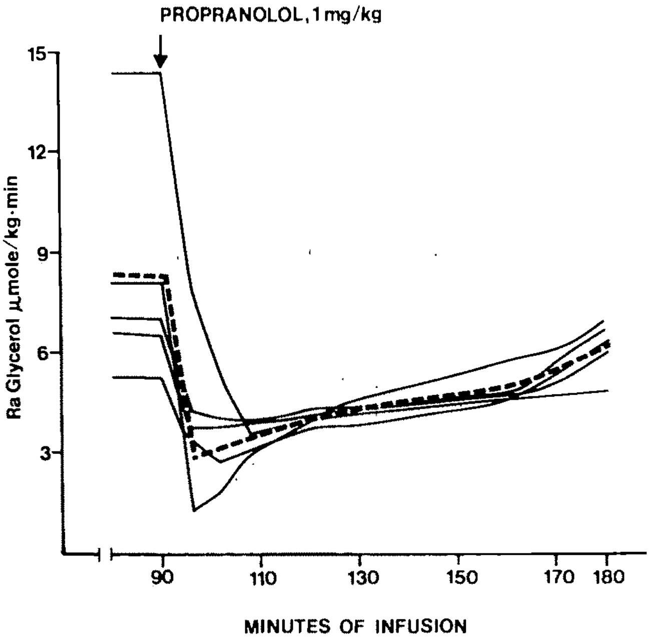

FIG. 3. Response of individual burned patients (solid lines) and mean response (dotted line) to the infusion of propranolol.

tients was higher than normal (mean basal value of 8.9 ± 1.6 μmol/kg/min *vs.* 2.2 ± 0.1 μmol/kg/min for normal adult volunteers, N = 8), the value was on average below the peak attained in normal volunteers fasted for 3 days and then infused with epinephrine at 0.015 μg/kg/min (16.0 ± 2.2 μmol/kg/min).[22] However, one nonresponding patient had a basal value of 17 μmol/kg/min (Fig. 1), and the other basal values of the nonresponders were also high when their limited amount of fat is considered. Although our body composition analysis was performed after recovery, and was thus not necessarily representative of the situation at the time of study, the extremely low percentage of body fat found at that time suggests the body fat mass was limiting in the extent to which lipolysis could be stimulated. This possibility is further supported by the fact that, at the time of study, the nonresponders had a greater amount of fat removed surgically than had those who responded to the epinephrine infusion (Table 3).

Despite the high basal rate of lipolysis in the burned children, the amount of FFA mobilized in the basal state was inadequate to meet energy requirements. The mean basal value of Ra FFA of all patients was 14.2 ± 1.2 μmol/kg/min. If all of this was completely oxidized, it would provide approximately 33 cal/kg/min of energy, assuming 17 carbons per fatty acid and 6.06 cal/mL of CO_2 produced (at an respiratory quotient of 0.70), whereas the overall mean value of basal energy expenditure was 36.4 ± 3.0 cal/kg/min. The inadequacy of Ra FFA to meet energy expenditure fully is further underscored by the fact that normally only 30–40% of Ra FFA is directly oxidized.[25] Since endogenously mobilized fat is the primary source of energy in the postabsorptive state, these severely burned children were in a negative energy balance of carbohydrate and/or protein at all times other than when they were receiving nutritional intake. Thus, it is of clinical interest that administration of beta-blockade had a paradoxical effect. Although it lowered the resting energy expenditure by approximately 6 cal/kg/min (Table 5), the reduction in potential energy available as a result of the fall in Ra FFA during beta-blockade was more than double the reduction in metabolic rate. Thus, beta-blockade would not be expected to have a beneficial effect on nitrogen metabolism in the postabsorptive state after burn injury, even though overall metabolic rate may be decreased. This prediction is consistent with evidence from an animal experiment.[26]

The failure of Ra FFA to increase in proportion to the increased rate of lipolysis in the burned patients is reflected by the low ratio of Ra FFA/Ra glycerol (1.6), compared with the normal value of approximately 3.[22] This is explained by an increased rate of re-esterification of fatty acids within the adipose tissue. Several factors favor a high rate of re-esterification in burn patients. Low serum albumin concentration is one factor. FFA are not soluble in water, and therefore must be transported in plasma bound to albumin. The normal molar ratio of FFA/albumin varies from 0.5 to 1.5.[27] In some patients, the albumin concentration was as low as 2.0 g/dL, or 0.29 μmol/mL, meaning that the FFA/albumin ratio was at the upper range, even though the concentration of FFA was below 0.5 μmol/mL. Not only was the albumin carrying capacity reduced in burned patients, but also the albumin availability most likely was reduced due to a sympathetic nervous system-induced vasoconstriction of blood flow in the fat. This would have no impact on Ra glycerol, since glycerol is dissolved in the water of plasma and the adipose tissue blood flow would not therefore be rate limiting. In contrast, decreased fat blood flow would limit Ra FFA and thus stimulate re-esterification. Also, plasma insulin concentration (and to a lesser extent, glucose concentration), were higher than normal in the patients. High insulin and/or glucose concentration favors re-esterification *in vivo* by increasing the availability of alpha-glycerol-phosphate.[7]

The high rate of re-esterification, coupled with the high rate of lipolysis, means that there was a high rate of triglyceride/fatty acid substrate cycling in burned patients. This high rate of substrate cycling may have contributed to the overall metabolic rate and could explain the apparent enhanced responsiveness to epinephrine infusion in the "responding" burn patients (Fig. 2). One important theoretical advantage of substrate cycling is amplification of control of substrate flux, provided that the Kmax of the enzymes are not approached.[28]

The clinical implication of these studies is that Ra FFA may be limited by the reduced amount of endogenous fat in severely burned children treated with excisional therapy, and this deficiency may have a negative impact on energy metabolism. Although fascial excision reduces the available fat mass and thus magnifies the problem of mobilization of adequate amounts of endogenous energy substrates, the findings of this study do not bear directly on the advisability of this surgical procedure for acute burn care, since with appropriate nutritional support it is possible to counteract any energy imbalance. The long-term effect of the removal of fat, on the other hand, may have important consequences in terms of rehabilitation, particularly with regard to the ability to perform exercise. With regard to the administration of adrenergic blocking agents to lower the metabolic rate, the findings of this study do not provide a metabolic basis for the procedure, since basal adrenergic activity plays a major role in stimulating lipolysis due to intact, or enhanced, lipolytic sensitivity to catecholamines.

Acknowledgments

The authors acknowledge the important contribution of Marta Wolfe for the mass spectrometry analyses. The technical assistance of Susan Fons, Esther Surriga, Glenn Chin, Nitina Seghal, and Boyd Carr was also greatly appreciated. The authors thank Thomas Rutan, R.N., for performing the indirect calorimetry, the nursing staff of the Shriners Burns Institute for help in performing the studies, and Judy Chadwick for typing the manuscript.

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Book Reviews

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Second Thoughts of a Surgical Curmudgeon. Mark M. Ravitch. 240 pp. Chicago: Year Book Medical Publishers. 1987. $12.95.

THE MOMENT THE prospective reader picks up this book and looks at the title, he becomes involved. Curmudgeon. While making mental note of its spelling, his analysis of the word as a title takes him to his dictionary. A school or pocket dictionary will only increase the mystery.

This is a remarkable and valuable book, full of wisdom, information, and stimulating new perspectives on many subjects close to the heart of students and graduates of medicine. It is written in the concise interesting style of this master writer and historian with some gentle humor and whimsy.

The book is a collection of 74 editorials, articles, and lectures by Ravitch, written between 1965 and 1984. The majority are brief and concise. Included is the full text of two superb lectures to the Alpha Omega Alpha. In one of these, for the first two thirds of his address, he apologizes to the audience for the inadequacies of their past education which, by design I am sure, would leave them totally "on side." Whereupon he quietly proceeds to deliver his message: "The focus must always be on the patient. Never lose sight of that." There is a fascinating piece of fiction with drama and suspense, published in *Esquire,* and a delightful spoof on "informed consent."

In selecting the contents, Mark Ravitch avoids science. The early sections deal principally with such subjects as Quality, Language, and Philosophy of a surgeon. Some were written in the late 1960s, of interest to historians and seniors. They are "not rewritten" and it is a sad commentary that many of the problems are still with us.

The later sections are more topical: Education, Medicosocial, and Ethics. Most were written in the 1980s. He is well informed and thought provoking. The patient in the hospital is a concern but he does not explore the concept or use the modern term "quality of life."

Dr. Ravitch's remarkable intellectual curiosity and perception comes through frequently. He tips his hand and tells the reader how he keeps abreast on such a wide front. There is practical advice on presenting and discussing papers and on the use of words. You should keep a dictionary nearby.

Dr. Ravitch's uniqueness is his breadth of interest and awareness of the past. The book is more than "second thoughts." It is an intimate portrait with special insight into the mind and character of a great American surgeon. This man of the prodigious mind is primarily human and involved.

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Surgery of the Small Intestine. Richard L. Nelson, Lloyd M. Nyhus. 592 pp. East Norwalk, Conn: Appleton-Century-Crofts. 1986. $110.00.

THIS WORK REPRESENTS a unique contribution to the field of gastrointestinal surgery, and the editors are to be complimented for providing us with a comprehensive text that deals with an often neglected subject; the small intestine. Our understanding of digestive physiology, intestinal motility, and gut hormones has been greatly expanded in recent years. This new knowledge has fostered a scientific and rational approach to the patient with intestinal disorders, and furthermore has facilitated the development of new and innovative surgical techniques for the management of serious gastrointestinal and genitourinary problems. The editors of *Surgery of the Small Intestine* have brought together an outstanding group of authors from diverse backgrounds and disciplines, with the final product being a state-of-the-art examination of small bowel physiology, pathophysiology, and treatment of associated surgical diseases.

The book is appropriately divided into nine sections with a total of 43 chapters. In addition, there are selected "Special Comments" following several chapters. These abbreviated discussions are focused on specific issues and add clarity and perspective to selected subjects. The detailed history at the beginning of the book is both stimulating and informative, and sets the stage for the elaborate review of small bowel anatomy and physiology that follows. The final chapter in this section deals with the metabolic consequences of ileal resection, a subject of vital importance to all general surgeons. The major disorders affecting the small bowel, in both pediatrics and adult populations, are reviewed in great detail in subsequent chapters. In addition, topics of considerable current clinical and investigative interest are explored, including small bowel transplantation, radiation enteritis, ileoanal pullthroughs, the use of ileal conduits in urology, and surgery for morbid obesity. Each chapter addresses the pertinent issues in terms of physiology and pathophysiology, management, and surgical options. There are several chapters devoted to technical aspects of bowel surgery, which are greatly enhanced by appropriate and well-done illustrations.

In general, the book is well written and easy to read. Drs. Nelson and Nyhus have attempted to write an authoritative text on the most diverse organ in the gastrointestinal tract. I believe they have been immensely successful. I strongly recommend this book for all students of the gastrointestinal tract, and all surgeons who have the occasion of dealing with the small bowel.

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Los Angeles, California

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Use in patients with bone marrow depression only when potential benefits outweigh risks. Patients who develop a hypersensitivity reaction (e.g., blood dyscrasias or jaundice) to a phenothiazine generally should not be reexposed to any phenothiazine. Caution patients about activities requiring alertness (e.g., operating vehicles or machinery), especially during the first few days' therapy. Prochlorperazine may intensify or prolong the action of other C.N.S. depressants.

Use in pregnancy is not recommended except in cases so serious and intractable that, in the physician's judgment, drug intervention is required and potential benefits outweigh possible hazards. There have been instances of prolonged jaundice, extrapyramidal signs, hyperreflexia or hyporeflexia in newborn infants whose mothers received phenothiazines. There is evidence that phenothiazines are excreted in the breast milk of nursing mothers.

Precautions: The antiemetic action of 'Compazine' may mask the signs and symptoms of overdosage of other drugs and may obscure the diagnosis and treatment of other conditions such as intestinal obstruction, brain tumor and Reye's syndrome (See Warnings). Postoperative aspiration of vomitus has occurred in a few surgical patients who received prochlorperazine as an antiemetic. When used concomitantly with cancer chemotherapeutic drugs, may obscure vomiting as a sign of these agents' toxicity. Deep sleep and coma have been reported with prochlorperazine, usually with overdosage.

Neuroleptic drugs cause elevated prolactin levels that persist during chronic administration. Since approximately one-third of human breast cancers are prolactin-dependent *in vitro*, this elevation is of potential importance if neuroleptic drug administration is contemplated in a patient with a previously detected breast cancer. Neither clinical nor epidemiologic studies to date, however, have shown an association between the chronic administration of neuroleptic drugs and mammary tumorigenesis.

Permanently stop neuroleptic therapy if neuromuscular reactions occur in pregnant women or in children.

In children with acute illnesses or dehydration, use only under close supervision. Avoid high doses and parenteral administration when cardiovascular system is impaired since hypotension has occurred. Use cautiously in patients with glaucoma. Use with caution in persons who will be exposed to extreme heat since phenothiazines may interfere with thermoregulatory mechanisms. Phenothiazines can diminish the effect of oral anticoagulants. Phenothiazines can produce alpha-adrenergic blockade. Thiazide diuretics may accentuate orthostatic hypotension that may occur with phenothiazines. Antihypertensive effects of guanethidine and related compounds may be counteracted when phenothiazines are used concomitantly. Concomitant administration of phenothiazines with propranolol results in increased plasma levels of both drugs and may also precipitate phenytoin toxicity. Phenothiazines may lower the convulsive threshold; dosage adjustments of anticonvulsants may be necessary. Presence of phenothiazines may produce false positive phenylketonuria (PKU) test results. Patients should not receive 'Compazine' 48 hours before or 24 hours after myelography with the contrast medium metrizamide.

Adverse Reactions: Drowsiness, dizziness, amenorrhea, blurred vision, skin reactions, Hypotension. Cholestatic jaundice, leukopenia, agranulocytosis. Fatty changes in the liver have been observed in a few patients who died while receiving the drug (no causal relationship has been established). Neuromuscular (extrapyramidal) reactions: motor restlessness, dystonias, pseudo-parkinsonism, tardive dyskinesia, and a variant, tardive dystonia. Contact dermatitis is a possibility if 'Compazine' Injection (solution) inadvertently gets on hands or clothing.

Other adverse reactions reported with 'Compazine' or other phenothiazines: Some adverse effects are more frequent or intense in specific disorders (e.g., severe hypotension in mitral insufficiency or pheochromocytoma). Grand mal and petit mal convulsions; altered cerebrospinal fluid proteins; cerebral edema; prolongation and intensification of the action of C.N.S. depressants, atropine, heat and organophosphorus insecticides; dryness of mouth, nasal congestion, headache, nausea, constipation, obstipation, adynamic ileus, ejaculatory disorders/impotence, priapism, atonic colon, urinary retention, miosis and mydriasis; reactivation of psychotic processes, catatonic-like states; hypotension (sometimes fatal); cardiac arrest; pancytopenia, thrombocytopenic purpura, eosinophilia, hemolytic anemia, aplastic anemia; biliary stasis; hyperglycemia, hypoglycemia, glycosuria, lactation, galactorrhea, gynecomastia, menstrual irregularities, false positive pregnancy tests; photosensitivity, itching, erythema, urticaria, eczema up to exfoliative dermatitis; asthma, laryngeal edema; angioneurotic edema, anaphylactoid reactions; peripheral edema; reversed epinephrine effect; hyperpyrexia; mild fever after large I.M. doses; increased appetite; increased weight; a systemic lupus erythematosus-like syndrome; pigmentary retinopathy; neuroleptic malignant syndrome, which may be fatal; with prolonged administration of substantial doses, skin pigmentation, epithelial keratopathy, and lenticular and corneal deposits.

EKG changes have been reported. Discontinue long-term, high-dose therapy gradually.

Note: Sudden death in patients taking phenothiazines (apparently due to cardiac arrest or asphyxia due to failure of cough reflex) has been reported.

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Letters to the Editor

December 1, 1986

Dear Editor:

In "Continuous Venous Oximetry in Surgical Patients" (Ann Surg 1986; 203:329–333.), Dr. Nelson has shown us a strong negative correlation between venous oxygen saturation (SvO_2) and the oxygen utilization coefficient (OUC). He has mathematically manipulated the Fick equation to show that "the determinants of SvO_2 are the components of oxygen delivery (DO_2) and oxygen consumption (VO_2)." Although the mathematics are not precisely correct, as they ignore the effect of dissolved gases, the relationship $SvO_2 = 1 - VO_2/DO_2$ is shown. Since VO_2/DO_2 is the definition of OUC, we see that $SvO_2 = 1 - OUC$. Therefore, the relationship shown in Figure 3D is mathematically ordained, and not the result of independent observations. Thus, any implication of a physiologic link (always risky with regression modeling) between SvO_2 and OUC that is based on those mathematically related observations is inappropriate. Perhaps, instead of concentrating on the closeness of the relationship, the author should have discussed the possible explanations for the deviation in Figure 3D from the mathematically predicted $y = 1 - x$. In any case it would appear that Dr. Nelson's conclusion that "SvO_2 does not correlate highly with the individual determinants of oxygen transport but rather correlates with the oxygen utilization coefficient and therefore reflects the overall balance between oxygen consumption and delivery" is not based on independent clinical observations. Regardless of the attractiveness of that hypothesis, the data in Dr. Nelson's study do not warrant that conclusion.

In spite of our disagreement with the analytic technique, we agree with Dr. Nelson's appraisal of the accuracy of mixed venous oximetry with the equipment described and of the clinical use of that measurement in a variety of critical care and intraoperative situations.

DAVID A. PAULUS, M.D.
RICHARD F. DAVIS, M.D.
Gainesville, Florida

January 20, 1987

Dear Editor:

Drs. Paulus and Davis are correct in their observations regarding the article "Continuous Venous Oximetry in Surgical Patients" (Ann Surg 1986; 203:329–333.). They point out that the contribution of dissolved oxygen to arterial and mixed venous oxygen content was ignored in the assumption that $SvO_2 = 1 - OUC$ (oxygen utilization coefficient). The dissolved oxygen content in blood (assuming reasonable hemoglobin concentration and arterial oxygen tension of less than 200 torr: both valid in these patients) is approximately 2% of total arterial content and 1% of mixed venous content. In conditions of hypoxemia and normal hemoglobin concentration, the contributions of dissolved oxygen are even less. These are negligible amounts with no clinical significance.

The derivation of the relationship $SvO_2 = 1 - OUC$ was presented in the discussion section of the article. Drs. Paulus and Davis are correct in noting that the relationship is "mathematically ordained." The question is can this link be clinically useful to the critical care surgeon?

OUC was calculated from arterial and mixed venous blood specimens, measurement of hemoglobin concentration, and thermodilution cardiac output. Since both hemoglobin and cardiac output can be factored out of the equation, the relationship is $OUC = SaO_2 - SvO_2/SaO_2$. Thus, continuous *in vivo* measurement of SvO_2 was compared with intermittent *in vitro* measurement of the determinants of SvO_2 (and the assumption that SaO_2 was high). What was shown in the article was that SvO_2 displayed continuously correlates closely with $1 - OUC$. Calculation of OUC by measurement of cardiac output, hemoglobin concentration, arterial and mixed venous oxygen saturation, and calculation of oxygen delivery and consumption requires both time and laboratory resources. If it is accepted that OUC is a useful means of assessing the oxygen supply–demand balance (a point not addressed in the article), then SvO_2 is a useful online monitor.

It is important to note that in critically ill surgical patients, a change in SvO_2 cannot be attributed reliably to any of the individual determinants of either oxygen delivery or oxygen consumption, a point often mistaken when reviewing other reports on this subject.

I thank Drs. Paulus and Davis for their interest.

LOREN D. NELSON, M.D.
Miami, Florida

January 20, 1987

Dear Editor:

Drs. Mackie, Hulks, and Cuschieri (Ann Surg 1986; 204:537–542) present evidence that confirms that gastric emptying is abnormal in patients with bile vomiting and conclude, like Toye and Alexander-Williams,[1] that altered gastric emptying is the cause of bile vomiting. We would submit that this study merely confirms an association of abnormal gastric emptying with bile vomiting, and this does not prove that the association is causal. A considerable amount of evidence leads us to believe that we should look elsewhere for the cause of bile vomiting; at least in a proportion of cases.

Bile vomiting occurs predominantly in patients who have had surgery for benign peptic ulcer. Such individuals are known to have a high prevalence of gastroesophageal reflux and esophagitis,[2] and abnormal gastric emptying is a common finding in patients with reflux.[3] The repeated effortless regurgitation of severe gastroesophageal reflux can be misinterpreted as vomiting by patient and clinician alike, and we have recent experience of two patients initially treated unsuccessfully for bile vomiting who became asymptomatic after effective fundoplication.

We are currently engaged in a study of all patients who have had surgery for bile vomiting in this department in the last 10 years, to determine the extent to which gastroesophageal reflux may have been responsible for their symptoms. Examination of the records of 25 such patients has shown that at least 10 (40%) had endoscopic signs of esophagitis before remedial surgery and four of these 10 had complications of esophagitis: two Barrett's esophagus and two esophageal strictures. Clinical and endoscopic follow-up is as yet incomplete, but we believe that these findings suggest strongly that the symptoms of a significant proportion of patients with "bile vomiting" are in fact due to gastroesophageal reflux.

The results of surgery for bile vomiting are less than ideal in most series,[4] and Ritchie has reported recently[5] that 35% of his patients continued to "vomit" after operation although the fluid disgorged was no longer bile stained. It would therefore be most interesting to know whether Mr. Mackie's patients had signs of gastroesophageal reflux on endoscopy or pH monitoring and to what extent his patients' symptoms have been relieved by treatment.

It is possible that in some patients grossly impaired gastric emptying could exacerbate gastroesophageal reflux. We suggest, however, that a careful assessment of gastroesophageal continence should be made before laying the blame for bile vomiting on delayed gastric emptying alone.

D. FLOOK
L. E. HUGHES
D. J. T. WEBSTER
Cardiff, Wales

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February 23, 1987

Dear Editor:

We appreciate the comments made by Mr. Flook et al. and confirm their view that esophagitis is a frequent accompaniment of bile vomiting, although we would dispute their contention that gastroesophageal reflux is the dominant mechanism responsible for bile vomiting. We have looked at our series of 97 patients with severe bile vomiting referred to AC over the past 17 years for remedial surgery. Biopsy-proven esophagitis was documented in 29-patients.

What is undeniable is that bile vomiting must be preceded by enterogastric reflux. This is usually present in patients after gastric surgery (excluding highly selective vagotomy) whether they vomit bile or not. Our recent study (Ann Surg 1986; 204:537–542) has demonstrated that the gastric emptying of this refluxate is delayed only in those patients who vomit bile. This is an undeniable fact that any other armchair hypothesis has to take into consideration. One could, indeed, argue that gastric retention would favor gastroesophageal reflux at least in some of these patients. Equally, however, the repeated vomiting may cause both the esophagitis and the gastroesophageal incompetence.

The suggestion made by Mr. Flook et al. that these patients should be investigated with pH monitoring is based on a false premise of "alkaline mucosal damage." We have studied 17 patients with bile vomiting and endoscopically proven esophagitis and have encountered "alkaline esophagitis" (reflux episodes of pH > 7.5) in only one patient; all the other 16 exhibited a normal pH profile in the lower esophagus during ambulatory 24-hour pH monitoring. These patients have presumably "neutral reflux" that cannot be detected by pH monitoring, and the damage may well be related to specific components within the refluxate (lysolecithin, bile salts, trypsin, *etc.*) rather than its alkalinity. In this respect we would suggest that reflux alkaline esophagitis is a myth.

A. CUSCHIERI
Dundee, Scotland

December 30, 1986

Dear Editor:

The paper, "An Analysis of Survival and Treatment Failure Following Abdominoperineal and Sphincter-saving Resection in Dukes' B and C Rectal Carcinoma. A Report of the NSABP Clinical Trials" by Drs. Wolmark and Fisher, in *Annals of Surgery* 1986; 204:480–489, contains a serious misimplication that requires correction.

The authors conclude in their abstract: "The data provide the first evidence from a randomized prospective clinical trial that sphincter-saving resection is not associated with attenuated survivorship or an increased incidence of treatment failure." Inherent in this statement is the implication that the surgical therapies of abdominoperineal excision or sphincter-saving resection of the rectum were randomized therapies. This was *not* the case, and hence this conclusion is *not* justified from their data. The cited reference in the current paper, describing ". . . in greater detail, protocol design and patient accession," does not define the operative conduct or protocol. Rather, it simply states "Patients with rectal tumors were treated with either anterior resection or abdominoperineal resection with the operative conduct determined by the protocol."[1] No further information is given as to how these two therapies were selected for patients from a larger undefined cohort.

To us as readers, this is a highly selected group of patients, who were legitimately randomized to adjuvant therapies after their surgical procedure; *however*, they cannot form the basis of a study as currently presented. The data apparently reflect a small part of the 85 Principle Investigator's experience, with less than one patient/year/investigator entered. The reader is not given information as to what factors, either rigid criteria or biases, determined which procedure was performed.

The misimplication that the surgical therapies were randomized was pointed out by two discussants of the paper (pp. 488–489), but despite this still remains in the text as presented in the Journal. The "abstract reader" or "skimmer" is left with the implication that this study evaluates these two operative methods in a randomized fashion. This implication is erroneous and should be corrected.

The original question posed by this randomized trial was the role of adjuvant therapy in patients after either of these surgical procedures. Randomization was performed after "curative resection." The authors have published five papers to date without addressing this primary question. Why? Randomized trials are an essential investigative method for testing therapeutic options; surely, the primary question should be addressed first. Additional information, such as data on the natural history of the disease, is often well documented in such studies because the patients are carefully followed and evaluated, but should be presented as secondary information.

The current paper does a serious disservice to prospective randomized clinical trials. Papers such as these are worthy of publication when presenting clinical experience. However, this paper presents no more than that, and should not masquerade as a randomized trial of two surgical therapies.

J. MICHAEL HENDERSON, F.R.C.S.
MICHAEL H. KUTNER, P.H.D.
Atlanta, Georgia

Reference

1. Wolmark N, Cruz I, Redmond CK, et al. Tumor size and regional lymph node metastasis in colorectal cancer: a preliminary analysis from the NSABP clinical trials. Cancer 1983; 51:1315–1322.

February 10, 1987

Dear Editor:

We are dismayed by Dr. Henderson and Kutner's assertion that we did not sufficiently emphasize the nature of the randomization in our reported study. The NSABP clinical trials assessing adjuvant therapy in colorectal cancer are well known. In fact, they are the largest clinical trials that have thus far been carried out in attempting to determine the utility of adjuvant therapy. Surgeons in particular are conversant with our studies since the majority of the 2500 patients randomized have been entered by surgeons. The specific aims of these studies as well as the randomization schemata are familiar to the majority of surgeons interested in colorectal cancer. As a consequence, the confusion expressed by Drs. Kutner and Henderson is difficult to understand.

Drs. Henderson and Kutner support their allegation by quoting a statement from our abstract: "the data provided the first evidence from a randomized prospective clinical trial that sphincter-saving resection is not associated with attenuated survivorship or an increased incidence of treatment failure." It is unclear why they failed to appreciate the statement in the abstract indicating that the analysis was derived from a randomized prospective clinical trial "designed to ascertain the efficacy of adjuvant therapy in rectal carcinoma (protocol R-01)." To dispel any potential confusion as to what the nature of the randomization was, a further description appeared in the introduction. We believe that the statement made was succinct and, accordingly, we reproduce it verbatim:

> In an effort to resolve some of the biologic and practical disputations surrounding the efficacy of sphincter-saving operations, it was considered appropriate to evaluate the data from the randomized prospective rectal cancer trial of the National Surgical Adjuvant Project for Breast and Bowel Cancer (NSABP). This study was primarily designed to evaluate the utility of adjuvant chemotherapy and radiotherapy following curative resection for Dukes' B and C cancer. Although the original specific aims of the study were not formulated to compare treatment failure and survival in patients treated with sphincter-saving resection and abdominoperineal resection, nonetheless a large patient cohort was available in whom the two operations were performed without specific protocol-determined selection bias. Despite this limitation, data were derived from patients treated with either procedure who were entered in a randomized prospective manner albeit not specifically for the end points considered in this analysis.

Further, to remove any doubt relative to the methodology it was pointed out that protocol R-01 consisted of "a randomized prospective clinical trial designed to determine the utility of adjuvant therapy in patients with carcinoma of the rectum." The nature of the study was further specified: "randomization was effected to three therapeutic categories: (1) no further treatment following curative resection, (2) postoperative radiotherapy or (3) postoperative chemotherapy consisting of 5-fluorouracil, MeCCNU (semustine) and vincristine."

Drs. Henderson and Kutner emphasize that two discussants of the oral presentation of the data (not the manuscript) alluded to the fact that randomization was not carried out between two operative options. It is our contention that the discussants had a clear understanding of the randomization procedure and, accordingly, for Drs. Kutner and Henderson to suggest that a "misapplication" had taken place is inappropriate. Drs. Kutner and Henderson elect to ignore the response made to the discussants' comments. Are Drs. Henderson and Kutner so unfamiliar with the state of the art in randomized prospective colorectal trials that they were actually mislead into assuming that a study had been done in which patients were randomized to sphincter ablation or sphincter preservation? In those few heroic attempts made to conduct such a study, accrual was nothing short of disastrous. Such a randomized prospective trial currently cannot be carried out nor is it likely that circumstances will arise to enable implementation of such a study in the foreseeable future. Given these constraints, we are insistent that our methodology represents the most accurate evaluation of the two operative interventions. Drs. Henderson and Kutner's confusion relative to the nature of this study is even more difficult to understand when one considers the second component of our investigation. We assessed disease-free survival and survival relative to the extent of margins achieved with anterior resections. To suggest that this analysis could be misconstrued as a study in which patients were randomized *a priori* to receive margins of <2 cm, 2–5 cm, and >5 cm challenges the imagination.

We take objection with the statement that patients who were entered into our randomized prospective clinical trial cannot form the basis of an analysis assessing sphincter-saving operations and abdominoperineal resections. We are perplexed by the logic in the assertion that natural history data derived from a randomized prospective trial should be presented only after the primary specific aims of the trial have been answered. It is our contention that these two goals are not mutually exclusive and both are worthy of longitudinal assessment and follow-up. Indeed, natural history information can be extremely useful in identifying discriminants for assessing interactions with treatment in proportional hazards models.

The suggestion that the data presented in our paper fall under the rubric of "clinical experience" is unworthy. Despite the fact that this trial did not randomize patients between sphincter-saving operations and abdominoperineal resections, the data were, nonetheless, derived from a prospective randomized trial. As with all NSABP trials quality control was carefully monitored and strictly enforced. Methodology was used to control for imbalances due to confounding variables. The data were controlled for Dukes' class, nodal status, and adjuvant therapy; no significant imbalances were observed with respect to age, preoperative CEA, or proportion of lumen encircled by tumor. To equate the quality of data derived from this prospective clinical trial with that of clinical experience consisting of anecdotal retrospective analyses using uncontrolled historic or concomitant nonrandomized controls is inappropriate. If Drs. Henderson and Kutner are perturbed by our methodology and relegate our data to the level of clinical experience, they must be chagrined at the plethora of anecdotal retrospective uncontrolled studies that constitute the mainstay of our most esteemed surgical journals.

Finally, it is laudable on the part of Drs. Kutner and Henderson to champion the lot of the "abstract reader" or "skimmer" and to protect him from the alleged misperception to be derived from our study. This posture raises philosophical and conceptual issues as to what constitutes the appropriate form of presenting data for publication in a journal of the calibre of the *Annals of Surgery*. Should one cater to the reader who peruses an occasional manuscript with half-hearted interest and attenuated concentration or should the manuscript be written for the surgeon who is able to review the paper in a critical and objective fashion? If favoring the latter approach constitutes a disservice to clinical trials, then we admit our guilt.

NORMAN WOLMARK, M.D.
BERNARD FISHER, M.D.
Pittsburgh, Pennsylvania

December 20, 1986

Dear Editor:

I was dismayed to read the study "EKG Guided Placement of Subclavian CVP Catheters Using J-Wire" (Ann Surg 1986; 204:673–676). The technique described is not only unnecessary but has significant potential for iatrogenic harm.

First of all, appropriate placement of central venous catheters can usually be determined clinically by a knowledge of surface anatomy and its relation to intrathoracic structures. The entry of the superior vena cava into the right atrium corresponds closely with the sternomanubrial joint (angle of Louis), which is nearly always palpable, or may be slightly caudad to the sternomanubrial joint within one intercostal space. The length of catheter necessary to traverse this distance can be easily estimated by realizing the course of the subclavian vein as it passes from the infraclavicular area to the mediastinum. I have personally used this technique for many years with good results.

Secondly, central venous catheters are often placed in patients with significant underlying problems, such as electrolyte imbalance, sepsis, ischemic heart disease, or cardiomyopathy, in which case the endocardium may be irritable and predisposed to complications thereof.

The authors' technique of manipulating central venous guidewires until arrhythmias were elicited is, to myself, both unnecessary and fraught with potential complications, especially when other reliable guides such as surface anatomy are available. The inherent arrhythmogenicity of central venous guidewires should encourage us to avoid their placement in the heart rather than purposefully seek it.

MICHAEL SWANSON, D.O.
Springfield, Missouri

February 20, 1987

Dear Editor:

Dr. Swanson's concerns are valid and his initial reaction to our technique understandable. We should look closely at the advantages and disadvantages of any new technique before considering its use in our own practice.

The advantages of the guidewire technique described in our article are that the presence of atrial arrhythmia is a reliable index of catheter tip location, resulting in 100% correct placement when present. The problem with unmonitored catheter placement is not the length of catheter, which can be approximated from surface anatomy, but the possibility of aberrant location, usually in the internal jugular vein.[1] Aberrant catheter location has been shown to produce incorrect CVP readings,[2] and can thus frustrate the basic reason for placing the catheter in the first place.

The main disadvantage of this technique is the potential for serious arrhythmia. Our current experience in 84 patients with significant ischemic heart disease confirms that of invasive cardiologists, the actual rate of morbidity caused by arrhythmia from intracardiac catheters and guidewires is surprisingly low.[3] This unexpected result perhaps renders this procedure more benign than it may appear at first sight.

In common with most procedures, the success rate in CVP catheter placement is of course operator dependent, and we would suggest consideration of this technique only for those physicians dissatisfied with their current results. Thus, not all physicians will have use for this technique, and those who do should bear in mind the importance of EKG monitoring and withdrawal of the guidewire if ventricular arrhythmia should occur.

DAVID S. STARR, M.D.
Youngstown, Ohio

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January 20, 1987

Dear Editor:

I would like to offer a few remarks concerning John Porter's article in which he states that reverse vein bypass grafts to distal vessels are superior to or equivalent to *in-situ* bypass grafts for patency and for vein utilization.

Dr. Porter continues to champion the reverse vein bypass graft and he now represents a minority view. His studies are elegant and must cause those of us who enthuse over *in-situ* grafting to keep a close eye on his long-term results. I switched to *in-situ* grafting in 1981 and have used a retrograde valvulotome for performing these grafts. This valvulotome is passed up the saphenous vein from the ankle to the groin without exposing the entire length of the saphenous vein. On withdrawal the valves are instantaneously incised, making this part of the operation very rapid. My cases are followed carefully and 4-year patency rates using the life table method are equivalent to those of Leather. In my hands at least, bypasses to the ankle using the reverse technique have not been feasible.

Be that as it may, and accepting Dr. Porter's thesis and his data, I must still quarrel with his conclusion in the final paragraph of his paper: "surgeons who achieve comparable results in their own practices should feel no pressure to switch to ISVB because of presumed superiority of the latter technique." Were the *in-situ* technique truly more complicated than the reverse technique, and if the results are truly equal, then Dr. Porter's point would be well taken. However, in point of fact, anyone who has been brought up on the *in-situ* technique finds it far simpler to do than the reverse technique. I suspect, then, that new surgeons, exposed to the *in-situ* technique, will also "feel no pressure" to switch to reverse vein grafting because of the presumed equivalency of the latter procedure.

In short, if the results are equal, why not choose the easier, *in-situ* technique?

GEORGE D. LEMAITRE, M.D.
Andover, Massachusetts

April 15, 1987

Dear Editor:

We are honored to reply to the points raised by Dr. LeMaitre regarding reversed *versus in situ* vein grafts. The author makes several statements in his letter including: (1) we, and others who perform reversed vein grafts, "represent a minority view," (2) the author has been unable to achieve satisfactory results with reversed vein bypass to the ankle, and (3) Dr. LeMaitre believes that anyone who has performed both techniques will find the *in situ* bypass easier to perform.

We are pleased that the author appears to accept our data that demonstrate at least equivalent patency figures for *in situ* and reversed bypass. We are not prepared to comment on the percentage of vascular surgeons in the United States using reversed or *in situ* grafts, as we have no specific data in this area. Likewise, we have no comment regarding the author's inability to achieve reversed vein grafts to the ankle level. This technique is routinely satisfactory for us and others who use the reversed vein technique.

With regard to the relative ease of performing either operation, we have several comments. It is our belief that any vein that can be used for *in situ* bypass can also be used with reversed technique. The converse of this statement, however, is not true. *In situ* bypass requires an intact greater saphenous vein. This means that the *in situ* operation must be confined to patients whose legs were not operated on previously. It is easy to understand the perception that the technique is easier if one confines operations exclusively to this "best case" patient group. In the patient group described in our paper, 33% of patients did not possess an intact ipsilateral greater saphenous vein, and would not have been eligible for *in situ* bypass. All these patients had successful revascularization using reverse technique. Adherence to the *in situ* technique automatically eliminates this important patient group, which in our experience is increasing in size, partly due to increasing numbers of patients referred after failed *in situ* bypass. Limiting lower extremity bypass to the *in situ* technique thus may be viewed from one aspect as a means to guarantee improved operative results by eliminating from consideration the group of patients (those previously operated on) in whom it will be most difficult to achieve successful lower extremity revascularization.

These considerations aside, however, it remains clear from abundant published evidence that equally skilled surgeons may be expected to obtain equivalent results with reversed or *in situ* vein grafts. Currently we are unaware of any evidence indicating clear superiority of one technique over the other. However, the reversed vein graft technique is applicable to significantly more patients, including the difficult patient group with failed previous bypasses. We are honored that Dr. LeMaitre found our article sufficiently provocative to warrant comment.

LLOYD M. TAYLOR, JR., M.D.
JAMES M. EDWARDS, M.D.
EDWARD S. PHINNEY, M.D.
JOHN M. PORTER, M.D.
Portland, Oregon

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The title page should contain [1] the title of the article, which should be concise but informative; [2] a short running head or footline of no more than 40 characters (count letters and spaces) placed at the foot of the title page and identified; [3] first name, middle initial, and last name of each author, with highest academic degree(s); [4] name of department(s) and institution(s) to which the work should be attributed; [5] disclaimers, if any; [6] name and address of author responsible for correspondence about the manuscript; [7] name and address of author to whom requests for reprints should be addressed, or statement that reprints will not be available from the author; [8] the source(s) of support in the form of grants, equipment, drugs, or all of these.

ABSTRACT AND KEY WORDS

The second page should carry an abstract of not more than 150 words. The abstract should state the purposes of the study or investigation, basic procedures (study subjects or experimental animals and observational and analytic methods), main findings (give specific data and their statistical significance, if possible), and the principal conclusions. Emphasize new and important aspects of the study or observations. Use only approved abbreviations (*see* list of Commonly Used Approved Abbreviations elsewhere in this document).

Key (indexing) terms: Below the abstract, provide and identify as such, three to 10 key words or short phrases that will assist indexers in cross-indexing your article and that may be published with the abstract. Use terms from the Medical Subject Headings list from *Index Medicus* whenever possible.

TEXT

The text of observational and experimental articles is usually—but not necessarily—divided into sections with the headings Introduction, Methods, Results, and Discussion. Long articles may need subheadings within some sections to clarify their content, especially the Results and Discussion sections. Other types of articles such as case reports, reviews, and editorials are likely to need other formats, and authors should consult individual journals for further guidance.

Introduction: Clearly state the *purpose* of the article. Summarize the rationale for the study or observation. Give only strictly pertinent references, and do not review the subject extensively.

Methods: Describe your selection of the observational or experimental subjects (patients or experimental animals, including controls) clearly. Identify the methods, apparatus (manufacturer's name and address in parentheses), and procedures in sufficient detail to allow other workers to reproduce the results. Give references to established methods, including statistical methods; provide references and brief descriptions of methods that have been published but are not well known; describe new or substantially modified methods, give reasons for using them, and evaluate their limitations.

When reporting experiments on human subjects, indicate whether the procedures followed were in accord with the ethical standards of the Committee on Human Experimentation of the institution in which the experiments were done or in accord with the Helsinki Declaration of 1975. When reporting experiments on animal subjects, indicate whether the institution's or the National Research Council's guide for the care and use of laboratory animals was followed. Identify precisely all drugs and chemicals used, including generic name(s), dosage(s), and route(s) of administration. Do not use patients' names, initials, or hospital numbers.

Include numbers of observations and the statistical significance of the findings when appropriate. Detailed statistical analyses, mathematical derivations, and the like may sometimes be suitably presented in the form of one or more appendixes.

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   Soter NA, Wasserman SI, Austen KF. Cold urticaria: release into the circulation of histamine and eosinophil chemotactic factor of anaphylaxis during cold challenge. N Engl J Med 1976; 294:687–90.

2. Corporate Author

   The Committee on Enzymes of the Scandinavian Society for Clinical Chemistry and Clinical Physiology. Recommended method for the determination of gammaglutamyltransferase in blood. Scand J Clin Lab Invest 1976; 36:119–25.

   Anonymous. Epidemiology for primary health care. Int J Epidemiol 1976; 5:224–5.

Books and Other Monographs

3. Personal Author(s)

   Osler AG. Complement: mechanisms and functions. Englewood Cliffs: Prentice-Hall, 1976.

4. Corporate Author

   American Medical Association Department of Drugs. AMA drug evaluations. 3rd ed. Littleton: Publishing Sciences Group, 1977.

5. Editor, Compiler, Chairman as Author

   Rhodes AJ, Van Rooyen CE, comps. Textbook of virology: for students and practitioners of medicine and the other health sciences. 5th ed. Baltimore: Williams & Wilkins, 1968.

6. Chapter in Book

   Weinstein L, Swartz MN. Pathogenic properties of invading microorganisms. In: Sodeman WA Jr, Sodeman WA, eds. Pathologic physiology: mechanisms of disease. Philadelphia: WB Saunders, 1974:457–71.

7. Agency Publication

   National Center for Health Statistics. Acute conditions: incidence and associated disability, United States July 1968–June 1969. Rockville, Md.: National Center for Health Statistics, 1972. (Vital and health statistics. Series 10: Data from the National Health Survey, no. 69) (DHEW publication no. (HSM)72-1036).

Other Articles

8. Newspaper Article

   Shaffer RA. Advances in chemistry are starting to unlock mysteries of the brain: discoveries could help cure alcoholism and insomnia, explain mental illness. How the messengers work. Wall Street Journal 1977 Aug 12:1(col. 1), 10(col. 1).

9. Magazine Article

   Roueché B. Annals of medicine: the Santa Claus culture. The New Yorker 1971 Sep 4:66–81.

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Omit internal horizontal and vertical rules.

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In most countries the International System of Units (SI) is standard or is becoming so. Report measurements in the units in which they were made. Journals may use these units, convert them to another system, or use both.

COMMONLY USED APPROVED ABBREVIATIONS

Standard Units of Measurement

Term	Abbreviation or Symbol
ampere	A
ångström	Å
barn	b
candela	cd
coulomb	C
counts per minute	cpm
counts per second	cps
curie	Ci
degree Celsius	°C
disintegration per minute	dpm
disintegration per second	dps
electron Volt	eV
equivalent	Eq
farad	F
gauss	G
gram	g
henry	H
hertz	Hz
hour	h
international unit	IU
joule	J
kelvin	K
kilogram	kg
liter, litre	l or L
meter, metre	m
minute	min
molar	*M*
mole	mol
newton	N
normal (concentration)	N
ohm	Ω
osmol	osmol
pascal	Pa
revolutions per minute	rpm
second	s
square centimeter	cm^2
volt	V
watt	W
week	wk
year	yr

Combining Prefixes

tera-	(10^{12})	T
giga-	(10^{9})	G
mega-	(10^{6})	M
kilo-	(10^{3})	k
hecto-	(10^{2})	h
deca-	(10^{1})	da
deci-	(10^{-1})	d
centi-	(10^{-2})	c

milli-	(10^{-3})	m
micro-	(10^{-6})	μ
nano-	(10^{-9})	n
pico-	(10^{-12})	p
femto-	(10^{-15})	f
atto-	(10^{-18})	a

Statistical Terms

correlation coefficient	r
degrees of freedom	df
mean	$\bar{x}$
not significant	NS
number of observations	n
probability	p
standard deviation	SD
standard error of the mean	SEM
"Student's" t test	*t* test
variance ratio	F

Others

adenosinediphosphatase	ADPase
adenosine 5′-diphosphate (adenosine diphosphate)	ADP
adenosine 5′-monophosphate (adenosine monophosphate, adenylic acid)	AMP
adenosine triphosphatase	ATPase
adenosine 5′-triphosphate (adenosine triphosphate)	ATP
adrenocorticotropic hormone (adrenocorticotropin)	ACTH
bacille Calmette-Guérin	BCG
basal metabolic rate	BMR
body temperature, pressure, and saturated	BTPS
central nervous system	CNS
coenzyme A	coA
deoxyribonucleic acid (deoxyribonucleate)	DNA
dihydroxyphenethylamine	dopamine
electrocardiogram	ECG
electroencephalogram	EEG
enteric cytopathogenic human orphan (virus)	ECHO
ethyl	Et
ethylenediaminetetraacetate	EDTA
gas-liquid chromatography	GLC
guanosine 5′-monophosphate (guanosine monophosphate, guanylic acid)	GMP
hemoglobin	Hb
logarithm (to base 10; common logarithm)	log
logarithm, natural	ln
methyl	Me
Michaelis constant	K_m
negative logarithm of hydrogen ion activity	pH
partial pressure of CO_2	P_{CO_2}
partial pressure of O_2	P_{O_2}
per	/
percent	%
radiation (ionizing, absorbed dose)	rad
respiratory quotient	RQ
specific gravity	sp gr
standard atmosphere	atm
standard temperature and pressure	STP
ultraviolet	uv
volume	vol
volume ratio (volume per volume)	vol/vol
weight	wt
weight per volume	wt/vol
weight ratio (weight per weight)	wt/wt

ABBREVIATIONS OF NAMES OF FREQUENTLY CITED JOURNALS

Acta Medica Scandinavica	Acta Med Scand
American Family Physician	Am Fam Physician
American Heart Journal	Am Heart J
American Journal of Cardiology	Am J Cardiol
American Journal of Clinical Nutrition	Am J Clin Nutr
American Journal of Clinical Pathology	Am J Clin Pathol
American Journal of Digestive Diseases	Am J Dig Dis
American Journal of Diseases of Children	Am J Dis Child
American Journal of Human Genetics	Am J Hum Genet
American Journal of the Medical Sciences	Am J Med Sci
American Journal of Medicine	Am J Med
American Journal of Obstetrics and Gynecology	Am J Obstet Gynecol
American Journal of Ophthalmology	Am J Ophthalmol
American Journal of Pathology	Am J Pathol
American Journal of Physical Medicine	Am J Phys Med
American Journal of Physiology	Am J Physiol
American Journal of Psychiatry	Am J Psychiatry
American Journal of Public Health	Am J Public Health
American Journal of Roentgenology	AJR
American Journal of Surgery	Am J Surg
American Journal of Tropical Medicine and Hygiene	Am J Trop Med Hyg
American Review of Respiratory Disease	Am Rev Respir Dis
Anaesthesia	Anaesthesia
Anesthesiology	Anesthesiology
Annals of Allergy	Ann Allergy
Annals of Internal Medicine	Ann Intern Med
Annals of Otology, Rhinology and Laryngology	Ann Otol Rhinol Laryngol
Annals of Surgery	Ann Surg
Annals of Thoracic Surgery	Ann Thorac Surg
Archives of Dermatology	Arch Dermatol
Archives of Environmental Health	Arch Environ Health
Archives of General Psychiatry	Arch Gen Psychiatry
Archives of Internal Medicine	Arch Intern Med
Archives of Neurology	Arch Neurol
Archives of Ophthalmology	Arch Ophthalmol
Archives of Otolaryngology	Arch Otolaryngol
Archives of Pathology and Laboratory Medicine	Arch Pathol Lab Med
Archives of Physical Medicine and Rehabilitation	Arch Phys Med Rehabil
Archives of Surgery	Arch Surg
Arthritis and Rheumatism	Arthritis Rheum
Blood; Journal of Hematology	Blood
Brain; Journal of Neurology	Brain
British Heart Journal	Br Heart J
British Journal of Obstetrics and Gynaecology	Br J Obstet Gynaecol
British Journal of Radiology	Br J Radiol
British Journal of Surgery	Br J Surg
British Medical Journal	Br Med J
Canadian Journal of Public Health	Can J Public Health
Canadian Medical Association Journal	Can Med Assoc J
Cancer	Cancer
Chest	Chest
Circulation; Journal of the American Heart Association	Circulation
Circulation Research	Circ Res
Clinical Pediatrics	Clin Pediatr (Phila)
Clinical Pharmacology and Therapeutics	Clin Pharmacol Ther
Clinical Science and Molecular Medicine	Clin Sci Mol Med
Clinical Toxicology	Clin Toxicol
Diabetes	Diabetes
DM, Disease-a-Month	DM
Endocrinology	Endocrinology
Gastroenterology	Gastroenterology
Geriatrics	Geriatrics
Gut	Gut
Human Pathology	Hum Pathol
Investigative Radiology	Invest Radiol
JAMA; Journal of the American Medical Association	JAMA
Journal of Allergy and Clinical Immunology	J Allergy Clin Immunol
Journal of Applied Physiology	J Appl Physiol
Journal of Biological Chemistry	J Biol Chem
Journal of Bone and Joint Surgery; American Volume	J Bone Joint Surg [Am]
Journal of Bone and Joint Surgery; British Volume	J Bone Joint Surg [Br]
Journal of Clinical Endocrinology and Metabolism	J Clin Endocrinol Metab
Journal of Clinical Investigation	J Clin Invest
Journal of Clinical Pathology	J Clin Pathol
Journal of Experimental Medicine	J Exp Med
Journal of Gerontology	J Gerontol
Journal of Immunology	J Immunol
Journal of Infectious Diseases	J Infect Dis
Journal of Investigative Dermatology	J Invest Dermatol
Journal of Laboratory and Clinical Medicine	J Lab Clin Med
Journal of Laryngology and Otology	J Laryngol Otol
Journal of Medical Education	J Med Educ
Journal of Nervous and Mental Disease	J Nerv Ment Dis
Journal of Neurosurgery	J Neurosurg
Journal of Pathology	J Pathol
Journal of Pediatrics	J Pediatr
Journal of Physiology	J Physiol
Journal of Thoracic and Cardiovascular Surgery	J Thorac Cardiovasc Surg
Journal of Trauma	J Trauma
Journal of Urology	J Urol
Lancet	Lancet
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Medicine (Baltimore)	Medicine (Baltimore)
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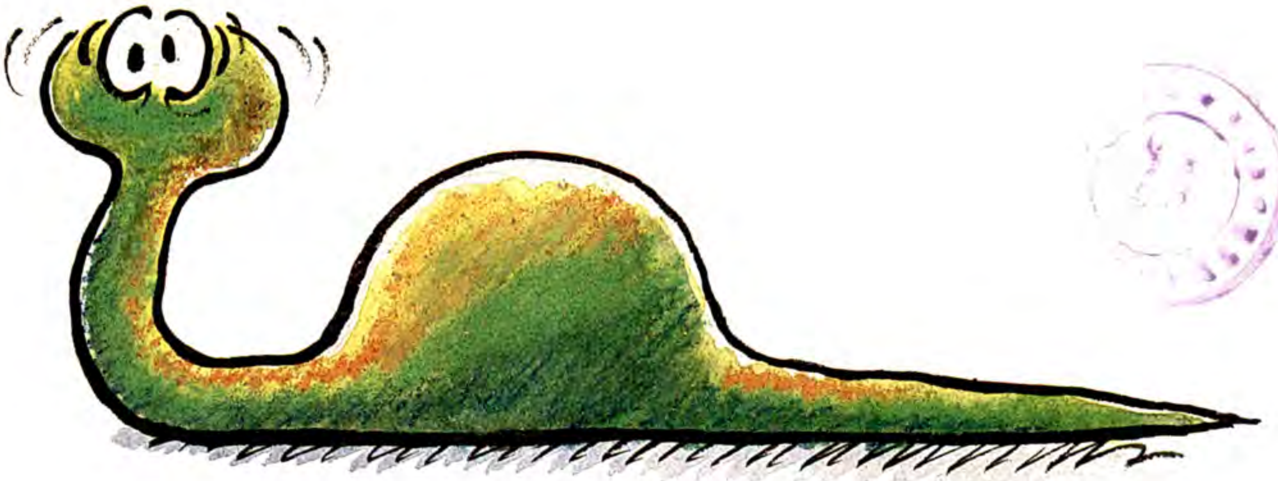

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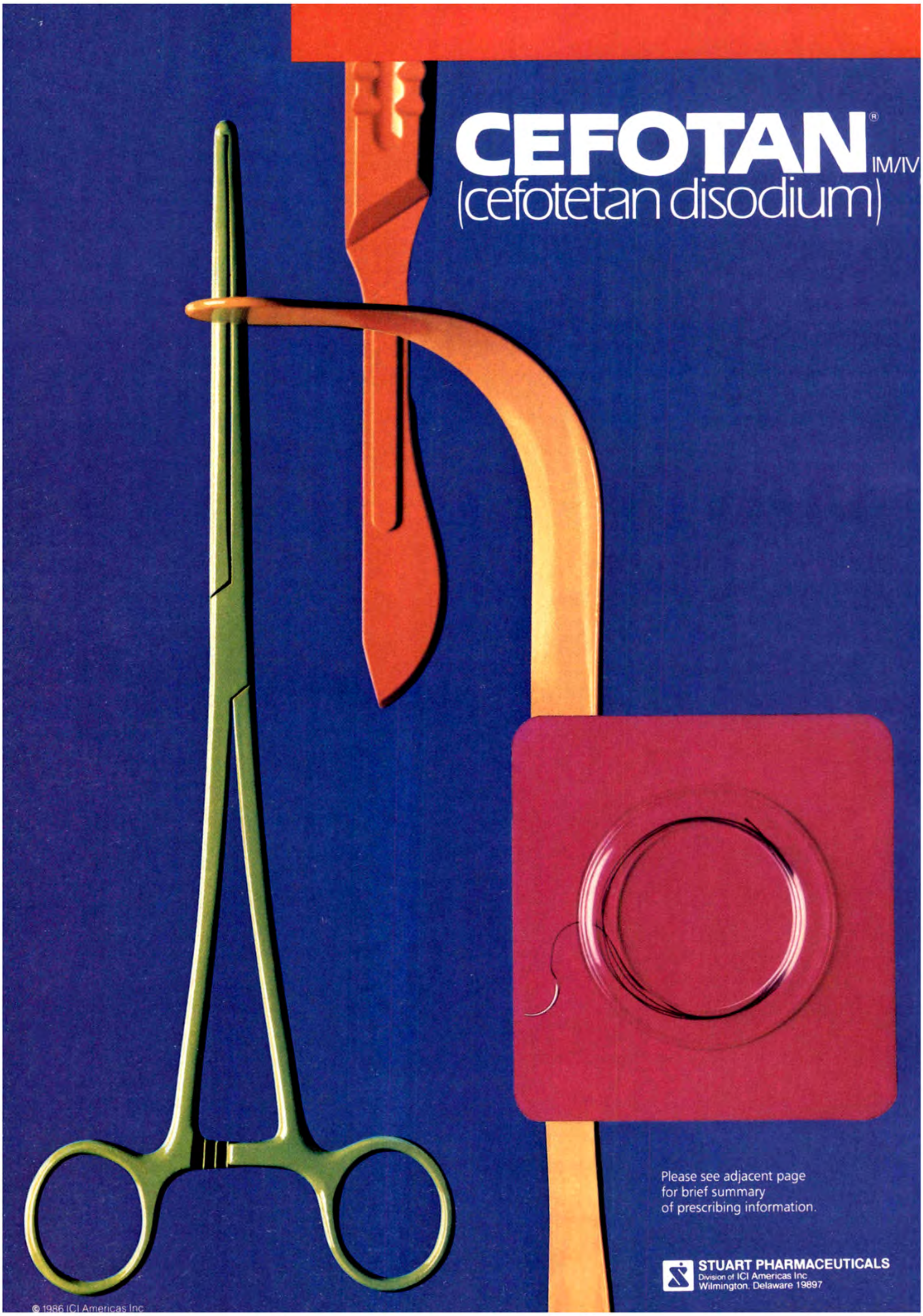

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BRIEF SUMMARY

INDICATIONS AND USAGE

TREATMENT: CEFOTAN® (cefotetan disodium) is indicated for the therapeutic treatment of the following infections when caused by susceptible strains of the designated organisms:

Urinary tract infections caused by *E coli*, *Klebsiella* species (including *K pneumoniae*), *Proteus mirabilis* and *Proteus* sp (which may include the organisms now called *Proteus vulgaris*, *Providencia rettgeri*, and *Morganella morganii*).

Lower respiratory tract infections caused by *Streptococcus pneumoniae* (formerly *D pneumoniae*), *Staphylococcus aureus* (penicillinase- and nonpenicillinase-producing strains), *Haemophilus influenzae* (including ampicillin-resistant strains), *Klebsiella* species (including *K pneumoniae*), and *E coli*.

Skin and skin structure infections caused by *Staphylococcus aureus* (penicillinase- and nonpenicillinase-producing strains), *Staphylococcus epidermidis*,[*] *Streptococcus pyogenes* and *Streptococcus* species (excluding enterococci), and *E coli*.

Gynecologic infections caused by *Staphylococcus aureus*[†] (including penicillinase- and nonpenicillinase-producing strains), *Staphylococcus epidermidis*,[*] *Streptococcus* species (excluding enterococci), *E coli*, *Proteus mirabilis*, *Neisseria gonorrhoeae*, *Bacteroides* species (excluding *B distasonis*, *B ovatus*, *B thetaiotaomicron*), *Fusobacterium* species,[†] and gram-positive anaerobic cocci (including *Peptococcus* and *Peptostreptococcus* species[†]).

Intra-abdominal infections caused by *E coli*, *Klebsiella* species (including *K pneumoniae*[†]), *Streptococcus* species (excluding enterococci), and *Bacteroides* species (excluding *B distasonis*, *B ovatus*, *B thetaiotaomicron*).

Bone and joint infections caused by *Staphylococcus aureus*.[†]

[*] **NOTE:** Some strains of *Staphylococcus epidermidis* are resistant to cefotetan.

[†] Efficacy for this organism in this organ system was studied in fewer than ten infections.

PROPHYLAXIS: The preoperative administration of CEFOTAN may reduce the incidence of certain postoperative infections in patients undergoing surgical procedures that are classified as clean contaminated or potentially contaminated (eg, cesarean section, abdominal or vaginal hysterectomy, transurethral surgery, biliary tract surgery, and gastrointestinal surgery).

The prophylactic dose of CEFOTAN should be administered 30 to 60 minutes prior to surgery. In patients undergoing cesarean section, CEFOTAN should be administered intravenously after the clamping of the umbilical cord.

If there are signs and symptoms of infection, specimens for culture should be obtained for identification of the causative organism so that appropriate therapeutic measures may be initiated.

CONTRAINDICATIONS

CEFOTAN is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

WARNINGS

Before therapy with CEFOTAN is instituted, careful inquiry should be made to determine whether the patient has had previous hypersensitivity reactions to cefotetan disodium, cephalosporins, penicillins, or other drugs. This product should be given cautiously to penicillin-sensitive patients. Antibiotics should be administered with caution to any patient who has demonstrated some form of allergy, particularly to drugs. If an allergic reaction to CEFOTAN occurs, discontinue the drug. Serious acute hypersensitivity reactions may require epinephrine and other emergency measures.

Pseudomembranous colitis has been reported with the use of cephalosporins (and other broad-spectrum antibiotics); therefore, it is important to consider its diagnosis in patients who develop diarrhea in association with antibiotic use.

Treatment with broad-spectrum antibiotics may alter normal flora of the colon and may permit overgrowth of clostridia. Studies indicate a toxin produced by *Clostridium difficile* is one primary cause of antibiotic-associated colitis. Cholestyramine and colestipol resins have been shown to bind the toxin in vitro.

Mild cases of colitis may respond to drug discontinuance alone. Moderate to severe cases should be managed with fluid, electrolyte, and protein supplementation as indicated. When the colitis is not relieved by drug discontinuance, or when it is severe, oral vancomycin is the treatment of choice for antibiotic-associated pseudomembranous colitis produced by *C difficile*. Other causes should also be considered.

PRECAUTIONS

GENERAL: As with other broad-spectrum antibiotics, prolonged use of CEFOTAN may result in overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection does occur during therapy, appropriate measures should be taken.

In common with many other broad-spectrum antibiotics, CEFOTAN may be associated with a fall in prothrombin activity. Those at risk include patients with renal or hepatic impairment, or poor nutritional state. Prothrombin times should be monitored in patients at risk and exogenous Vitamin K administered as indicated.

CEFOTAN should be used with caution in individuals with a history of gastrointestinal disease, particularly colitis.

INFORMATION FOR PATIENTS: As with some other cephalosporins, a disulfiram-like reaction characterized by flushing, sweating, headache, and tachycardia may occur when alcohol (beer, wine, etc) is ingested within 72 hours after CEFOTAN administration. Patients should be cautioned about the ingestion of alcoholic beverages following the administration of CEFOTAN.

DRUG INTERACTIONS: If CEFOTAN and an aminoglycoside are used concomitantly, renal function should be carefully monitored, especially if higher dosages of the aminoglycoside are to be administered or if therapy is prolonged, because of the potential nephrotoxicity and ototoxicity of aminoglycoside antibiotics. Although, to date, nephrotoxicity has not been noted when CEFOTAN was given alone, it is possible that nephrotoxicity may be potentiated if CEFOTAN is used concomitantly with an aminoglycoside.

DRUG/LABORATORY TEST INTERACTIONS: A false positive reaction for glucose in urine may occur with Benedict's or Fehling's solution.

As with other cephalosporins, high concentrations of cefotetan may interfere with measurement of serum and urine creatinine levels of Jaffe reaction and produce false increases in the levels of creatinine reported.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY: Although long-term studies in animals have not been performed to evaluate carcinogenic potential, no mutagenic potential of cefotetan was found in standard laboratory tests.

Cefotetan has adverse effects on the testes of prepubertal rats. Subcutaneous administration of 500 mg/kg/day (approx 8-16 times the usual adult human dose) on days 6-35 of life (thought to be developmentally analogous to late childhood and prepuberty in humans) resulted in reduced testicular weight and seminiferous tubule degeneration in 10 of 10 animals. Affected cells included spermatogonia and spermatocytes; Sertoli and Leydig cells were unaffected. Incidence and severity of lesions were dose-dependent; at 120 mg/kg/day (approx 2-4 times the usual human dose), only 1 of 10 treated animals was affected, and the degree of degeneration was mild. Similar lesions have been observed in experiments of comparable design with other methylthiotetrazole-containing antibiotics and impaired fertility has been reported, particularly at high dose levels. No testicular effects were observed in 7-week-old rats treated with up to 1000 mg/kg/day SC for 5 weeks, or in infant dogs (3 weeks old) that received up to 300 mg/kg/day IV for 5 weeks. The relevance of these findings to humans is unknown.

USAGE IN PREGNANCY: Pregnancy Category B: Reproduction studies have been performed in rats and monkeys at doses up to 20 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to cefotetan. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

USAGE IN NURSING MOTHERS: Cefotetan is excreted in human milk in very low concentrations. Caution should be exercised when cefotetan is administered to a nursing woman.

PEDIATRIC USE: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

In clinical studies the following adverse effects were considered related to CEFOTAN therapy.

Gastrointestinal symptoms occurred in 1.5 percent of patients; the most frequent were diarrhea (1 in 80) and nausea (1 in 700).

Hematologic laboratory abnormalities occurred in 1.4 percent of patients and included eosinophilia (1 in 200), positive direct Coombs' test (1 in 250), and thrombocytosis (1 in 300).

Hepatic enzyme elevations occurred in 1.2 percent of patients and included a rise in SGPT (1 in 150), SGOT (1 in 300), alkaline phosphatase (1 in 700), and LDH (1 in 700).

Hypersensitivity reactions were reported in 1.2 percent of patients and included rash (1 in 150) and itching (1 in 700).

Local effects were reported in less than one percent of patients and included phlebitis at the site of injection (1 in 300), and discomfort (1 in 500).

DOSAGE AND ADMINISTRATION

TREATMENT: The usual adult dosage is 1 or 2 grams of CEFOTAN administered intravenously or intramuscularly every 12 hours for 5 to 10 days. Proper dosage and route of administration should be determined by the condition of the patient, severity of the infection, and susceptibility of the causative organism.

GENERAL GUIDELINES FOR DOSAGE OF CEFOTAN

Type of Infection	Daily Dose	Frequency and Route
Urinary Tract	1-4 grams	500 mg every 12 hours IV or IM 1 or 2 g every 24 hours IV or IM 1 or 2 g every 12 hours IV or IM
Other Sites	2-4 grams	1 or 2 g every 12 hours IV or IM
Severe	4 grams	2 g every 12 hours IV
Life-Threatening	6* grams	3 g every 12 hours IV

*Maximum daily dosage should not exceed 6 grams.

PROPHYLAXIS: To prevent postoperative infection in clean contaminated or potentially contaminated surgery in adults, the recommended dosage is 1 or 2 g of CEFOTAN administered once, intravenously, 30 to 60 minutes prior to surgery. In patients undergoing cesarean section, the dose should be administered as soon as the umbilical cord is clamped.

IMPAIRED RENAL FUNCTION: When renal function is impaired, a reduced dosage schedule must be employed. The following dosage guidelines may be used.

DOSAGE GUIDELINES FOR PATIENTS WITH IMPAIRED RENAL FUNCTION

Creatinine Clearance mL/min	Dose	Frequency
>30	Usual Recommended Dose*	Every 12 hours
10-30	Usual Recommended Dose*	Every 24 hours
<10	Usual Recommended Dose*	Every 48 hours

*Dose determined by the type and severity of infection, and susceptibility of the causative organism.

Cefotetan is dialyzable and it is recommended that for patients undergoing intermittent hemodialysis, one-quarter of the usual recommended dose be given every 24 hours on days between dialysis and one-half the usual recommended dose on the day of dialysis.

HOW SUPPLIED

CEFOTAN is a dry, white to pale yellow powder supplied in vials containing cefotetan disodium equivalent to 1 g and 2 g cefotetan activity for intravenous and intramuscular administration. The 1 g dose is available in 10 mL and 100 mL vials, and the 2 g dose is available in 20 mL and 100 mL vials. The vials should not be stored at temperatures above 22°C and should be protected from light.

1 g in 10 mL vial (NDC 0038-0376-10)
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INDICATIONS AND USAGE: For the relief of moderate to moderately severe pain.
CONTRAINDICATIONS: Hypersensitivity to acetaminophen or hydrocodone.
WARNINGS
Drug Abuse and Dependence: VICODIN is subject to the Federal Controlled Substances Act (Schedule III). Psychic dependence, physical dependence and tolerance may develop upon repeated administration of narcotics; therefore, VICODIN should be prescribed and administered with the same caution appropriate to the use of other oral-narcotic-containing medications.
Respiratory Depression: At high doses or in sensitive patients, hydrocodone may produce dose-related respiratory depression by acting directly on brain stem respiratory centers. Hydrocodone also affects centers that control respiratory rhythm, and may produce irregular and periodic breathing.
Head Injury and Increased Intracranial Pressure: The respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a preexisting increase in intracranial pressure. Furthermore, narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries.
Acute Abdominal Conditions: The administration of narcotics may obscure the diagnosis or clinical course of patients with acute abdominal conditions
PRECAUTIONS
Special Risk Patients: VICODIN should be used with caution in elderly or debilitated patients and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, prostatic hypertrophy or urethral stricture.
Information for Patients: VICODIN, like all narcotics, may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery; patients should be cautioned accordingly.
Cough Reflex: Hydrocodone suppresses the cough reflex; caution should be exercised when VICODIN is used postoperatively and in patients with pulmonary disease.
Drug Interactions: The CNS-depressant effects of VICODIN may be additive with that of other CNS depressants. When combined therapy is contemplated, the dose of one or both agents should be reduced. The use of MAO inhibitors or tricyclic antidepressants with hydrocodone preparations may increase the effect of either the antidepressant or hydrocodone. The concurrent use of anticholinergics with hydrocodone may produce paralytic ileus.
Usage in Pregnancy: Pregnancy Category C. Hydrocodone has been shown to be teratogenic in hamsters when given in doses 700 times the human dose. There are no adequate and well-controlled studies in pregnant women. VICODIN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
Nonteratogenic Effects: Babies born to mothers who have been taking opioids regularly prior to delivery will be physically dependent. The intensity of the syndrome does not always correlate with the duration of maternal opioid use or dose.
Labor and Delivery: Administration of VICODIN to the mother shortly before delivery may result in some degree of respiratory depression in the newborn, especially if higher doses are used.
Nursing Mothers: It is not known whether this drug is excreted in human milk; therefore, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.
Pediatric Use: Safety and effectiveness in children have not been established.
ADVERSE REACTIONS
Central Nervous System: Sedation, drowsiness, mental clouding, lethargy, impairment of mental and physical performance, anxiety, fear, dysphoria, dizziness, psychic dependence, mood changes.
Gastrointestinal System: Nausea and vomiting may occur; they are more frequent in ambulatory than in recumbent patients. Prolonged administration of VICODIN may produce constipation.
Genitourinary System: Ureteral spasm, spasm of vesical sphincters and urinary retention have been reported.
Respiratory Depression: (See WARNINGS.)
DOSAGE AND ADMINISTRATION: Dosage should be adjusted according to the severity of the pain and the response of the patient. However, tolerance to hydrocodone can develop with continued use, and the incidence of untoward effects is dose related. The usual dose is one tablet every six hours as needed for pain. (If necessary, this dose may be repeated at four-hour intervals.) In cases of more severe pain, two tablets every six hours (up to eight tablets in 24 hours) may be required.
Revised, April 1982. 5685

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HYDROCODONE		X			X
CODEINE	X	X	X	X	X
OXYCODONE	XX	XX	XX	XX	XX

Blank space indicates that no such activity has been reported.

Table adapted from Facts and Comparisons (Nov.) 1984 and Catalano RB. The medical approach to management of pain caused by cancer. "Semin Oncol" 1975; 2; 379-92 and Reuler JB, et. al. The chronic pain syndrome: misconceptions and management. "Ann Intern Med" 1980; 93; 588-96.

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1. Hopkinson JH III: *Curr Ther Res* 24: 503-516, 1978
2. Beaver, WT *Arch Intern Med,* 141:293-300, 1981.

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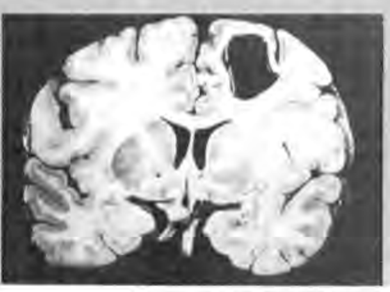

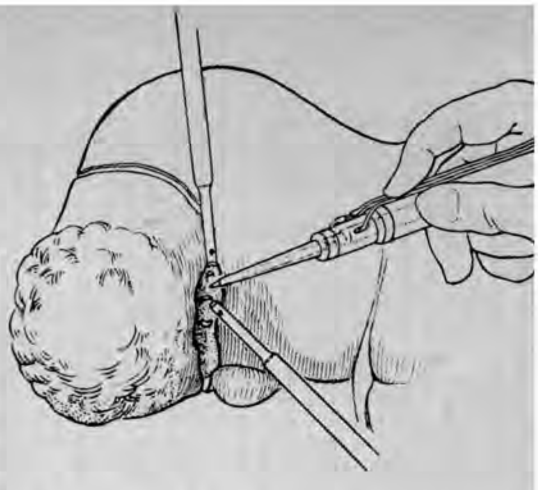

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Edited by Steven A. Rosenberg, M.D., Ph.D.

Chief of Surgery, National Cancer Institute, Bethesda, MD.
9 contributors.

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Before prescribing, please see full prescribing information. A Brief Summary follows:

Thrombostat must not be injected! Apply on the surface of bleeding tissue as a solution or powder.

INDICATIONS AND USAGE: Thrombostat (Thrombin, USP) is indicated as an aid in hemostasis wherever oozing blood from capillaries and small venules is accessible.

In various types of surgery solutions of Thrombostat may be used in conjunction with Absorbable Gelatin Sponge, USP for hemostasis.

CONTRAINDICATIONS: Thrombostat is contraindicated in persons known to be sensitive to any of its components and/or to material of bovine origin.

WARNING: Because of its action in the clotting mechanism, Thrombostat must not be injected or otherwise allowed to enter large blood vessels. Extensive intravascular clotting and even death may result. Thrombostat is an antigenic substance and has caused sensitivity and allergic reactions when injected into animals.

PRECAUTIONS: General: Consult the absorbable gelatin sponge product labeling for complete information for use prior to utilizing the thrombin-saturated-sponge procedure.

Pregnancy—Teratogenic effects: Pregnancy Category C. Animal reproduction studies have not been conducted with Thrombin, Topical (Bovine). It is also not known whether Thrombin, Topical (Bovine) can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Thrombin, Topical (Bovine) should be given to a pregnant woman only if clearly indicated.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: An allergic type reaction following the use of Thrombostat for treatment of epistaxis has been reported. Febrile reactions have also been observed following the use of Thrombostat in certain surgical procedures but no cause-effect relationship has been established.

DOSAGE AND ADMINISTRATION: General: Solutions of Thrombostat may be prepared in sterile distilled water or isotonic saline. The intended use determines the strength of the solution to prepare. For general use in plastic surgery, dental extractions, skin grafting, neurosurgery, etc, solutions containing approximately 100 units per ml are frequently used. For this, 10 ml of diluent added to the 1000 unit package is suitable. Where bleeding is profuse, as from cut surfaces of liver and spleen, concentrations as high as 1000 to 2000 units per ml may be required. For this the 5000 unit vial dissolved in 5 ml or 2.5 ml respectively, of the diluent supplied in the package is convenient. Intermediate strengths to suit the needs of the case may be prepared by selecting the proper strength package and dissolving the contents in an appropriate volume of diluent. In many situations, it may be advantageous to use Thrombostat (Thrombin, USP) in dry form on oozing surfaces.

Caution: Solutions should be used the day they are prepared. The solution may be used for up to 6 hours when stored at room temperature; up to 24 hours when stored under refrigeration, and, if necessary, up to 48 hours when stored frozen.

The following techniques are suggested for the topical application of Thrombostat.

1. The recipient surface should be sponged (not wiped) free of blood before Thrombostat is applied.
2. A spray may be used or the surface may be flooded using a sterile syringe and small gauge needle. The most effective hemostasis results when the Thrombostat mixes freely with the blood as soon as it reaches the surface.
3. In instances where Thrombostat in dry form is needed, the vial is opened by removing the metal ring by flipping up the plastic cap and tearing counterclockwise. The rubber-diaphragm cap may be easily removed and the dried Thrombostat is then broken up into a powder by means of a sterile glass rod or other suitable sterile instrument.
4. Sponging of treated surfaces should be avoided in order that the clot remain securely in place.

Thrombostat may be used in conjunction with Absorbable Gelatin Sponge, USP as follows:

1. Prepare Thrombostat solution of the desired strength.
2. Immerse sponge strips of the desired size in the Thrombostat solution. Knead the sponge strips vigorously with moistened gloved fingers to remove trapped air, thereby facilitating saturation of the sponge.
3. Apply saturated sponge to bleeding area. Hold in place for 10 to 15 seconds with a pledget of cotton or a small gauze sponge.

Thrombostat Kit: Thrombostat Kit contains one sterile 20,000 unit vial of Thrombostat, one sterile vial of Isotonic Saline Diluent, and one sterile pump sprayer cap. The Kit may be used as follows:

1. Remove the Tyvek blister lid by pulling up at the indicated corner. The sterile inner tray can be lifted out or introduced into the operating field.
2. The cover to the sterile inner tray is removed by pulling up on the finger tab, exposing the sterile contents.
3. Thrombostat solution of the desired strength is prepared and the pump sprayer cap inserted and seated on the Thrombostat solution vial. Note: Several strokes of the pump sprayer will be required before the Thrombostat solution is expelled.
4. Alternatively, when Thrombostat in dry form is needed, the vial is opened as described above and the dried Thrombostat broken up into a powder by means of a sterile glass rod or other suitable sterile instrument.

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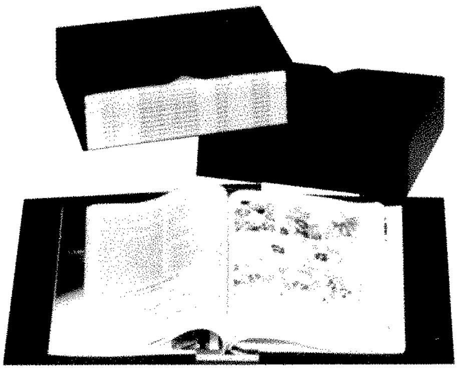

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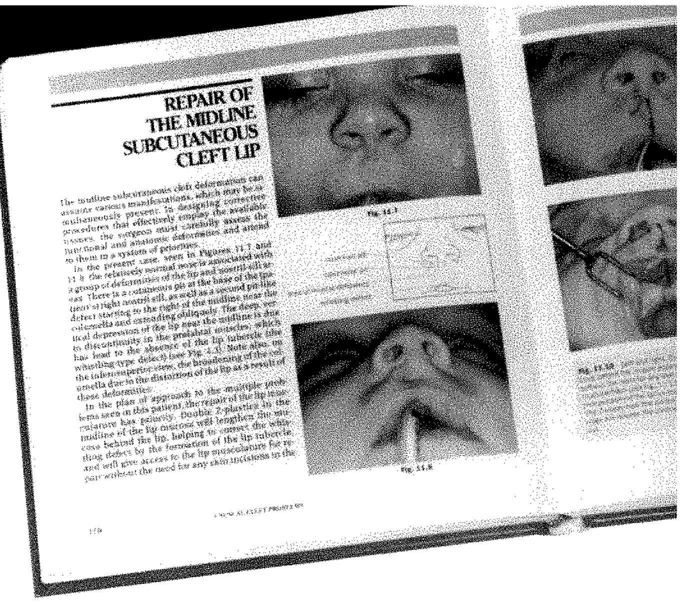
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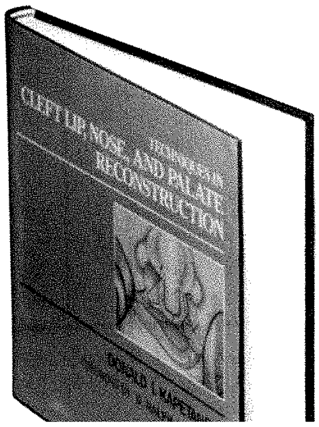

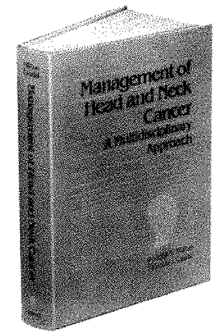
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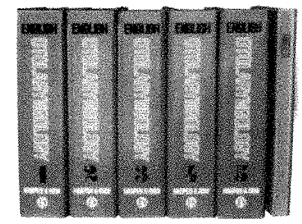

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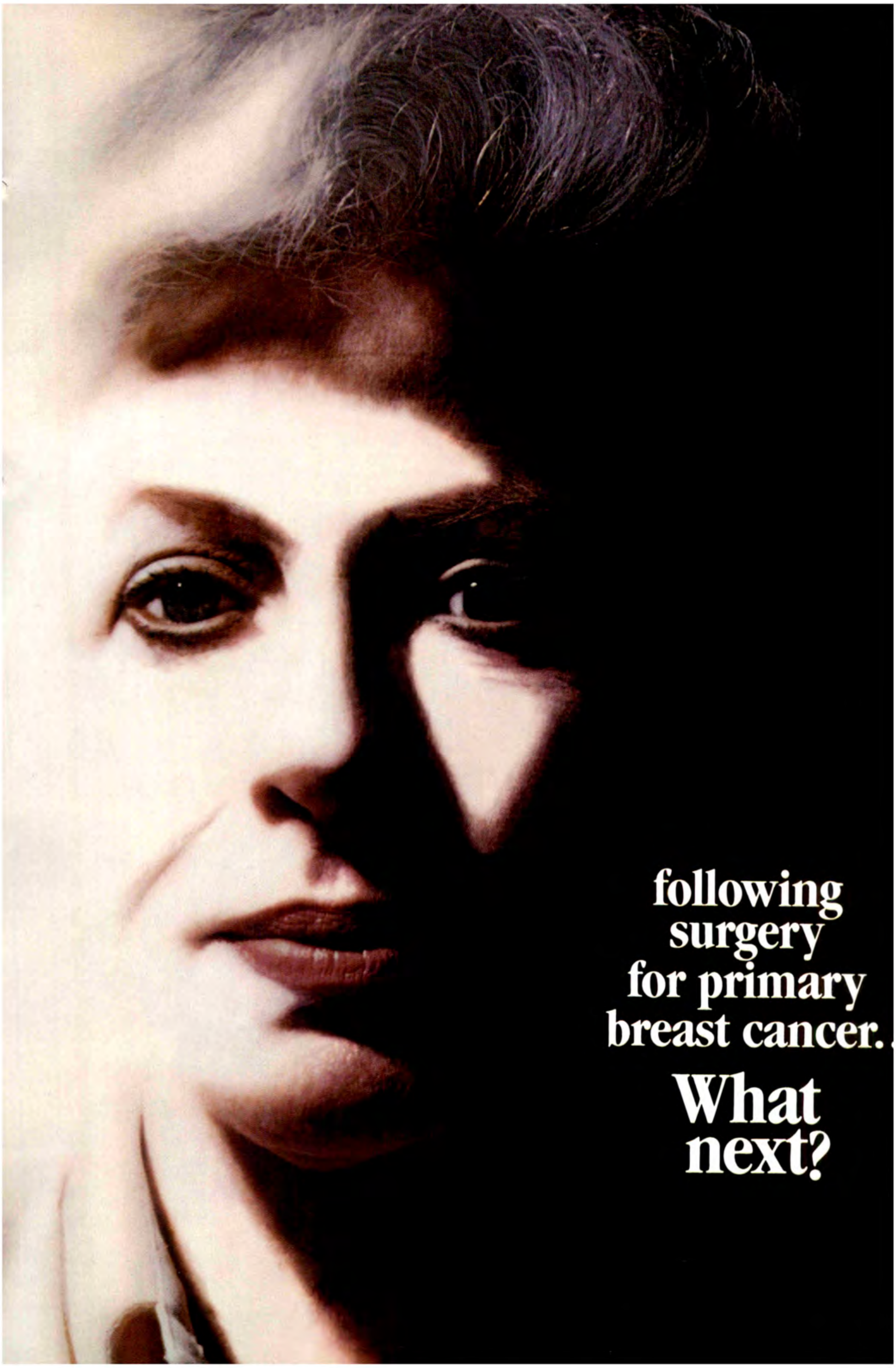

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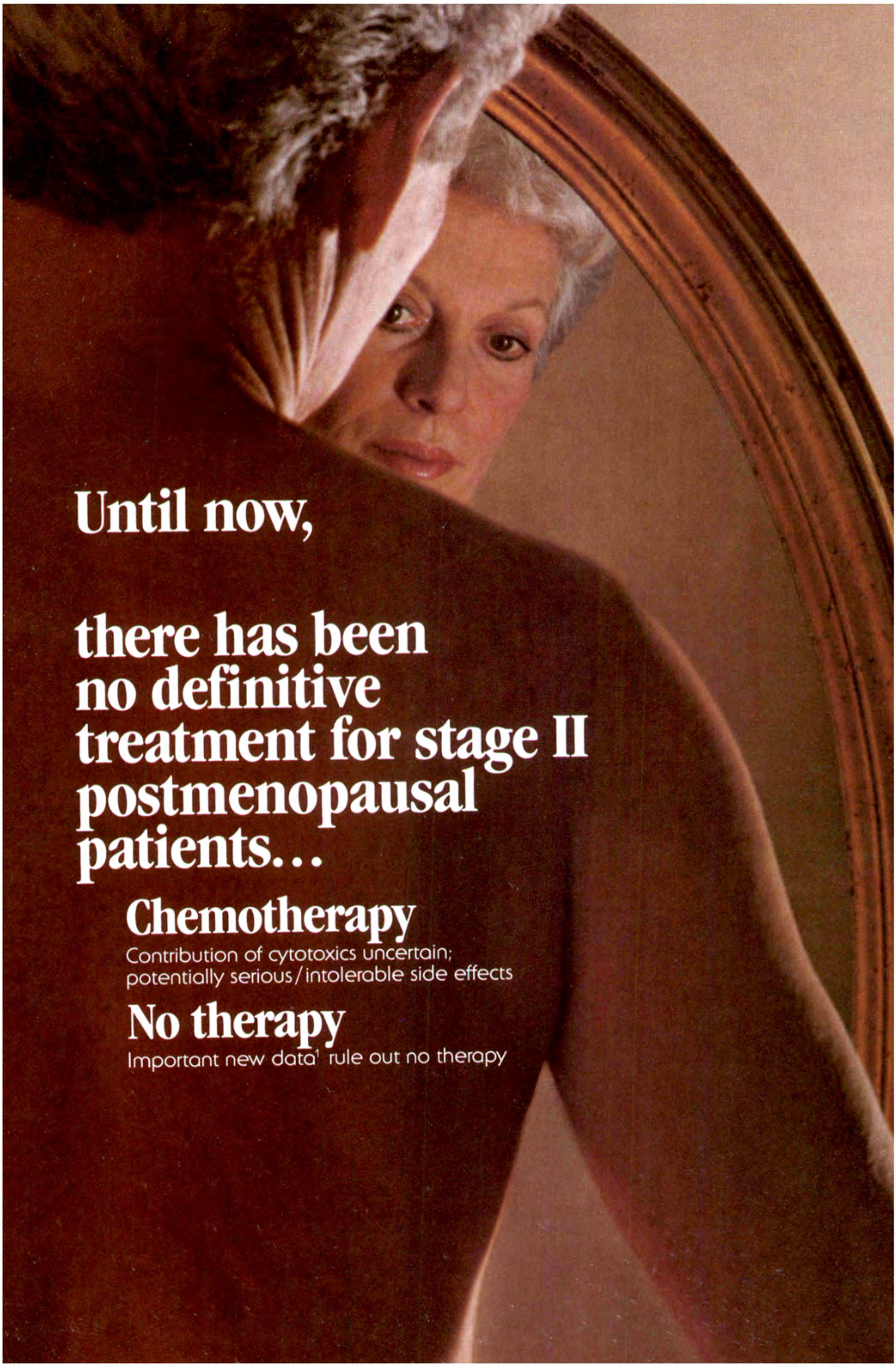

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Please see next page for brief summary of prescribing information.

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BRIEF SUMMARY

INDICATIONS AND USAGE: NOLVADEX is effective in the treatment of metastatic breast cancer in postmenopausal women. Available evidence indicates that patients whose tumors are estrogen receptor positive are more likely to benefit from NOLVADEX therapy.

NOLVADEX is effective in delaying recurrence following total mastectomy and axillary dissection in postmenopausal women with breast cancer (T1-3, N1, M0). The estrogen and progesterone receptor values may help to predict whether NOLVADEX therapy is likely to be beneficial. In some NOLVADEX adjuvant studies, most of the benefit to date has been in the subgroup with 4 or more positive axillary nodes.

CONTRAINDICATIONS: None known.

WARNINGS: Pregnancy Category D: NOLVADEX may cause fetal harm when administered to a pregnant woman. Individuals should not become pregnant while taking NOLVADEX. Effects on reproductive functions are expected from the antiestrogenic properties of the drug. In reproductive studies in rats at dose levels equal to or below the human dose, nonteratogenic developmental skeletal changes were seen and were found to be reversible. In addition, in fertility studies in rats and in teratology studies in rabbits using doses at or below those used in humans, a lower incidence of embryo implantation and a higher incidence of fetal death or retarded in utero growth were observed, with slower learning behavior in some rat pups. The impairment of learning behavior did not achieve statistical significance in one study, and, in another study where significance was reported, this was by comparing dosed animals with controls of another study. Several pregnant marmosets were dosed during organogenesis or in the last half of pregnancy. No deformations were seen and although the dose was high enough to terminate pregnancy in some animals, those that did maintain pregnancy showed no evidence of teratogenic malformations. There are no adequate and well controlled studies in pregnant women. There have been reports of spontaneous abortions, birth defects, fetal deaths, and vaginal bleeding. If this drug is used during pregnancy or the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

Ocular changes have been reported in a few patients who, as part of a clinical trial, were treated for periods greater than one year with NOLVADEX at doses at least four times the highest recommended daily dose of 40 mg. The ocular changes consist of retinopathy and, in some patients, there are also corneal changes and a decrease in visual acuity.

In addition, a few cases of ocular changes including visual disturbance, corneal changes, and/or retinopathy have been reported in patients treated with NOLVADEX at recommended doses. It is uncertain if these effects are due to NOLVADEX.

As with other additive hormonal therapy (estrogens and androgens), hypercalcemia has been reported in some breast cancer patients with bone metastases within a few weeks of starting treatment with NOLVADEX. If hypercalcemia does occur, appropriate measures should be taken and, if severe, NOLVADEX should be discontinued.

PRECAUTIONS: General: NOLVADEX should be used cautiously in patients with existing leukopenia or thrombocytopenia. Observations of leukopenia and thrombocytopenia occasionally have been made, but it is uncertain if these effects are due to NOLVADEX therapy. Transient decreases in platelet counts, usually to 50,000-100,000/cu mm, infrequently lower, have been occasionally reported in patients taking NOLVADEX for breast cancer. No hemorrhagic tendency has been recorded and the platelet counts returned to normal levels even though treatment with NOLVADEX continued.

Laboratory Tests: Periodic complete blood counts, including platelet counts, may be appropriate.

Carcinogenesis: While no conventional bioassay has been conducted, endocrine changes in immature and mature mice were investigated in a 13-month study. Granulosa cell ovarian tumors and interstitial cell testicular tumors were found in mice receiving NOLVADEX, but not in the controls.

Mutagenesis: No genotoxic potential has been found in a battery of in vivo and in vitro tests with pro- and eukaryotic test systems with drug metabolizing systems present.

Impairment of Fertility: Fertility in female rats was decreased following administration of 0.04 mg/kg for 2 weeks prior to mating through day 7 of pregnancy. There was a decreased number of implantations, and all fetuses were found dead.

Following administration to rats of 0.16 mg/kg from days 7-17 of pregnancy, there were increased numbers of fetal deaths. Administration of 0.125 mg/kg to rabbits during days 6-18 of pregnancy resulted in abortion or premature delivery. Fetal deaths occurred at higher doses. There were no teratogenic changes in either rat or rabbit segment II studies. Several pregnant marmosets were dosed with 10 mg/kg/day either during organogenesis or in the last half of pregnancy. No deformations were seen, and, although the dose was high enough to terminate pregnancy in some animals, those that did maintain pregnancy showed no evidence of teratogenic malformations. Rats given 0.16 mg/kg from day 17 of pregnancy to 1 day before weaning demonstrated increased numbers of dead pups at parturition. It was reported that some rat pups showed slower learning behavior, but this did not achieve statistical significance in one study, and in another study where significance was reported, this was by comparing dosed animals with controls of another study.

The recommended daily human dose of 20-40 mg corresponds to 0.4-0.8 mg/kg for an average 50 kg woman.

Pregnancy Category D: See WARNINGS.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from NOLVADEX, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

ADVERSE REACTIONS: The most frequent adverse reactions to NOLVADEX are hot flashes, nausea and vomiting. These may occur in up to one-fourth of patients, but are rarely severe enough to require discontinuation of treatment.

Less frequently reported adverse reactions are vaginal bleeding, vaginal discharge, menstrual irregularities and skin rash. Usually these have not been of sufficient severity to require dosage reduction or discontinuation of treatment.

Increased bone and tumor pain and, also, local disease flare have occurred, which are sometimes associated with a good tumor response. Patients with increased bone pain may require additional analgesics. Patients with soft tissue disease may have sudden increases in the size of preexisting lesions, sometimes associated with marked erythema within and surrounding the lesions and/or the development of new lesions. When they occur, the bone pain or disease flare are seen shortly after starting NOLVADEX and generally subside rapidly.

Other adverse reactions which are seen infrequently are hypercalcemia, peripheral edema, distaste for food, pruritus vulvae, depression, dizziness, light-headedness and headache. There have been infrequent reports of thromboembolic events occurring during NOLVADEX therapy. Since for cancer patients in general an increased incidence of thromboembolic events is known to occur, a causal relationship to NOLVADEX remains conjectural. An increased incidence has been reported when cytotoxins are combined with NOLVADEX.

If adverse reactions are severe, it is sometimes possible to control them by a simple reduction of dosage without loss of control of the disease.

OVERDOSAGE: Acute overdosage in humans has not been reported. Signs observed at the highest doses following studies to determine LD_{50} in animals were respiratory difficulties and convulsions. No specific treatment for overdosage is known; treatment must be symptomatic.

DOSAGE AND ADMINISTRATION: One or two 10 mg tablets twice a day (morning and evening). In the three single agent adjuvant NOLVADEX studies noted above (See Clinical Pharmacology), NOLVADEX was administered for two years. The optimal duration of adjuvant therapy is not known.

HOW SUPPLIED: Tablets containing tamoxifen as the citrate in an amount equivalent to 10 mg of tamoxifen (round, biconvex, uncoated, white tablet identified with NOLVADEX 600 debossed on one side and a cameo debossed on the other side) are supplied in bottles of 60 tablets and 250 tablets. Protect from heat and light.

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INDICATIONS For the relief of moderate to severe pain. NUBAIN can also be used for preoperative analgesia, as a supplement to surgical anesthesia, and for obstetrical analgesia during labor.

CONTRAINDICATIONS NUBAIN should not be administered to patients who are hypersensitive to it.

WARNINGS Drug Dependence NUBAIN has been shown to have a low abuse potential which is approximate to that of pentazocine. When compared with drugs which are not mixed agonist-antagonists, it has been reported that nalbuphine's potential for abuse would be less than that of codeine and propoxyphene. Psychological and physical dependence and tolerance may follow the abuse or misuse of nalbuphine. Therefore, caution should be observed in prescribing it for emotionally unstable patients, or for individuals with a history of narcotic abuse. Such patients should be closely supervised when long-term therapy is contemplated. Care should be taken to avoid increases in dosage or frequency of administration which in susceptible individuals might result in physical dependence. Abrupt discontinuation of NUBAIN following prolonged use has been followed by symptoms of narcotic withdrawal, i.e., abdominal cramps, nausea and vomiting, rhinorrhea, lacrimation, restlessness, anxiety, elevated temperature and piloerection. **Use in Ambulatory Patients** NUBAIN may impair the mental or physical abilities required for the performance of potentially dangerous tasks such as driving a car or operating machinery. Therefore, NUBAIN should be administered with caution to ambulatory patients who should be warned to avoid such hazards. **Use in Emergency Procedures** Maintain patient under observation until recovered from NUBAIN effects that would affect driving or other potentially dangerous tasks. **Use in Children** Clinical experience to support administration to patients under 18 years is not available at present. **Use in Pregnancy (other than labor)** Safe use of NUBAIN in pregnancy has not been established. Although animal reproductive studies have not revealed teratogenic or embryotoxic effects, nalbuphine should only be administered to pregnant women when, in the judgement of the physician, the potential benefits outweigh the possible hazards. **Use During Labor and Delivery** NUBAIN can produce respiratory depression in the neonate. It should be used with caution in women delivering premature infants. **Head Injury and Increased Intracranial Pressure** The possible respiratory depressant effects and the potential of potent analgesics to elevate cerebrospinal fluid pressure (resulting from vasodilation following CO_2 retention) may be markedly exaggerated in the presence of head injury, intracranial lesions or a pre-existing increase in intracranial pressure. Furthermore, potent analgesics can produce effects which may obscure the clinical course of patients with head injuries. Therefore, NUBAIN should be used in these circumstances only when essential, and then should be administered with extreme caution. **Interaction With Other Central Nervous System Depressants** Although NUBAIN possesses narcotic antagonist activity, there is evidence that in nondependent patients it will not antagonize a narcotic analgesic administered just before, concurrently, or just after an injection of NUBAIN. Therefore, patients receiving a narcotic analgesic, general anesthetics, phenothiazines, or other tranquilizers, sedatives, hypnotics, or other CNS depressants (including alcohol) concomitantly with NUBAIN may exhibit an additive effect. When such combined therapy is contemplated, the dose of one or both agents should be reduced. **Sulfites Sensitivity** NUBAIN contains sodium metabisulfite, a sulfite that may cause allergic-type reactions (e.g., hives, itching, wheezing, anaphylaxis) in certain susceptible persons. Although the overall prevalence of sulfite sensitivity in the general population is probably low, it is seen more frequently in asthmatics or in atopic nonasthmatic persons.

PRECAUTIONS Impaired Respiration At the usual adult dose of 10 mg/70 kg, NUBAIN causes some respiratory depression approximately equal to that produced by equal doses of morphine. However, in contrast to morphine, respiratory depression is not appreciably increased with higher doses of NUBAIN. Respiratory depression induced by NUBAIN can be reversed by NARCAN® (naloxone hydrochloride) when indicated. NUBAIN should be administered with caution at low doses to patients with impaired respiration (e.g., from other medication, uremia, bronchial asthma, severe infection, cyanosis or respiratory obstructions). **Impaired Renal or Hepatic Function** Because NUBAIN is metabolized in the liver and excreted by the kidneys, patients with renal or liver dysfunction may overreact to customary doses. Therefore, in these individuals, NUBAIN should be used with caution and administered in reduced amounts. **Myocardial Infarction** As with all potent analgesics, NUBAIN should be used with caution in patients with myocardial infarction who have nausea or vomiting. **Biliary Tract Surgery** As with all narcotic analgesics, NUBAIN should be used with caution in patients about to undergo surgery of the biliary tract since it may cause spasm of the sphincter of Oddi.

ADVERSE REACTIONS The most frequent adverse reaction in 1066 patients treated with NUBAIN is sedation 381 (36%). Less frequent reactions are sweaty/clammy 99 (9%); nausea/vomiting 68 (6%); dizziness/vertigo 58 (5%); dry mouth 44 (4%); and headache 27 (3%). Other adverse reactions which may occur (reported incidence of 1% or less) are: **CNS Effects** Nervousness, depression, restlessness, crying, euphoria, floating, hostility, unusual dreams, confusion, faintness, hallucinations, dysphoria, feeling of heaviness, numbness, tingling, unreality. The incidence of psychotomimetic effects, such as unreality, depersonalization, delusions, dysphoria and hallucinations has been shown to be less than that which occurs with pentazocine. **Cardiovascular** Hypertension, hypotension, bradycardia, tachycardia. **Gastrointestinal** Cramps, dyspepsia, bitter taste. **Respiration** Depression, dyspnea, asthma. **Dermatological** Itching, burning, urticaria. **Miscellaneous** Speech difficulty, urinary urgency, blurred vision, flushing and warmth. **Patients Dependent on Narcotics** Patients who have been taking narcotics chronically may experience withdrawal symptoms upon the administration of NUBAIN. If unduly troublesome, narcotic withdrawal symptoms can be controlled by the slow intravenous administration of small increments of morphine, until relief occurs. If the previous analgesic was morphine, meperidine, codeine, or other narcotic with similar duration of activity, one-fourth of the anticipated dose of NUBAIN can be administered initially and the patient observed for signs of withdrawal, i.e., abdominal cramps, nausea and vomiting, lacrimation, rhinorrhea, anxiety, restlessness, elevation of temperature or piloerection. If untoward symptoms do not occur, progressively larger doses may be tried at appropriate intervals until the desired level of analgesia is obtained with NUBAIN. **Management of Overdosage** The immediate intravenous administration of NARCAN® (naloxone hydrochloride) is a specific antidote. Oxygen, intravenous fluids, vasopressors and other supportive measures should be used as indicated. The administration of single doses of 72 mg of NUBAIN subcutaneously to eight normal subjects has been reported to have resulted primarily in symptoms of sleepiness and mild dysphoria.

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Presidential Address: The Craft of Surgery, Its Changing Face

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IN HIS ADDRESS to this Association in 1969, Owen Wangensteen remarked that the Presidential Address should be an annual lectureship on the status, outlook, and vistas of surgery.[1] Today I propose to review the status and outlook for surgery, with special reference to what I consider the craft of surgery and with particular attention to my own interest: neurologic surgery.

Momentous events in the last century and a half have shaped the face of surgery, its science and its craft, even though surgery is still basically the use of hands and tools to modify or eliminate malfunction and disease to prolong life and enhance its quality and dignity. Shires described the last half of the 19th century as the third surgical renaissance that laid the foundation for modern surgery, beginning with ether and chloroform anesthesia in 1848, followed by the work of Pasteur and Lister leading to antisepsis and asepsis for surgical wounds.[2] There followed a century of remarkable growth in the technical aspects of surgery, including the advances resulting from experience in two world wars. Every body cavity and viscus were invaded for the eradication of disease or the repair of injury. But the modern zenith of surgery came only after World War II with the introduction of antibiotics and the development of surgical biology—Shires fourth surgical renaissance—wherein surgical technology advanced incredibly on the basis of increasing knowledge of human physiology and chemistry and their maintenance or restoration. But other events, occurring even now, are changing the face of surgery again.

A year ago, a newspaper writer asked what effect would occur in neurosurgery because of the use of endovascular balloon techniques by diagnostic radiologists. He had been told that within a decade neurosurgeons would no longer be operating on intracranial aneurysms, a challenging technical surgical problem to which I and many others had devoted much of our working lives.

I well remember the shudder that went through the neurosurgical world in 1974 when Serbinenko, a Moscow neurosurgeon, published his paper first describing endovascular detachment of occluding balloons in the large arterial feeders to cerebral arteriovenous malfor-

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mations (AVMs). He also had treated two aneurysms by the technique that he refused to disclose. Soon thereafter a few neuroradiologists developed their own techniques, most notably Debrun et al.[3] in Paris and Kerber[4] in Oregon. As our neuroradiologists, including Debrun who joined our unit in 1978, had been deeply involved with such techniques, including the calibrated leak balloon, I was well aware of the state of the art, its potential, and its problems.

A report about the work of the neuroradiologists seemed, at first, to call for a neurosurgical response to the blanket dismissal of neurosurgical treatment of aneurysms. There was no question that the diagnostic radiologists who had moved into interventional radiology were exerting a profound influence in many of surgery's anatomic fields. It was equally true that their skills and results had been advancing steadily in the decade or so after the introduction of balloon technology. However, the neurosurgical success rate for ruptured aneurysms was well over 90% for patients in reasonable condition. Thus, the journalistic predictions of imminent demise of neurosurgical treatment seemed overdrawn.

A surgeon chooses his surgical discipline for differing reasons. For neurosurgery, it seemed to me that no other tissue handled by surgeons was so delicately eloquent and fragile, or demanded such elegant, precise technical skill and gentleness. Operations had to be based on an intimate knowledge of cerebral structure and function, and for no other tissue was there more to be learned. This challenge to the use of hands and instruments of the day was significant in my choice of a surgical career over 40 years ago. Surgeons take deep personal pleasure in helping patients by operative measures and the intensity of the feeling varies directly with the gravity of the disorder, the risk of the surgical invasion, and the balance between risk and the potential for cure.

For this occasion, I have been stimulated to look back over the changes in the craft of neurosurgery and in other surgical sciences occurring over one surgical lifetime in North America since World War II. Even in a cursory survey of this period, it is obvious that many profound changes in the face of surgery have occurred and are continuing to do so. On the one hand these changes may limit certain surgical actions in the classical sense but may at the same time provide broad horizons for expansion. Except for some matters related to government and the law, most changes have benefited the surgical patient. There can be no surgeon in this audience whose work and thought have not been affected profoundly by these events.

Most advances in medicine and general medical technology have an effect on surgery. Who of us has not indelibly imprinted in his memory the first time, near the end of World War II, when we gained access to a vial of dark yellow penicillin generally used for a patient with an overwhelming staphylococcal infection. Our memory of the first computed tomographic (CT) scan is vivid too, and for neurosurgeons, so is the first look at an aneurysm under the microscope.

We may group the changes under three broad headings: (1) general, (2) pharmacology, (3) technology.

General Changes

The social transformation of medicine by government, industry, and third parties has already begun to have some effect on the details of how surgical operations are performed. Insistences on outpatient surgery, for example, is a clear entry into the judgmental decision of the surgeon and may influence significantly the quality of surgical care. Obsession with cost containment and the threat of civil action for unsatisfactory outcome may drive certain procedures and areas of practice into specialized units or even restrict their performance under any circumstances. This is most visible in obstetrics where specialists are abandoning its practice since there is little prospect for relief from enormous penalties after delivery of impaired children, no matter the reason.

The expansionist strivings of limited licensed practitioners and occasional surgeons, such as partially trained family practitioners, are not likely to have a major impact on surgical craftsmanship. However, in a few institutions, podiatrists have been given privileges for major operations on the foot and ankle joints, even up to the knee. The effect on quality may be left to the imagination.

Both the quality and distribution of surgical care are influenced by manpower factors, which have been concerns of this Association and of both the American and Canadian Colleges of Surgeons. If surgical manpower rises so as to diminish appreciably the operative experience of the average surgeon, we could see a diminution in quality from this factor alone. The Study on Surgical Services for the United States (SOSSUS) reported in 1975 that surgical operative loads were light, measured against a presumed optimal level. In the Rhode Island Study[5] the operative work load for general surgeons dropped from 1970 to 1977, whereas the surgeon-to-population ratio rose 22%.

MacLean's study of his surgical staff suggests that Canadian surgeons, nearly all of whom are certified and who number about one-third less per capita than in the United States (30/100,000 Canada *vs.* 51/100,000 U.S.), were reaching acceptable levels, averaging 2900 California relative value scale units (CRV) per annum, probably a low estimate since a few had large research time allotments.[6] Of interest is that English and Welsh surgeons who number about one sixth per capita of the United States and one fourth of Canadian surgeons, have the potential for very high workloads.[7] Overall, they number 7.7/100,000, but there are only two consultant general surgeons per 100,000 population. However, there is a considerable but varying dilution of these large workloads by senior surgical registrars.

SOSSUS, while recommending that the number of physicians performing operations should be decreased and the number of procedures performed by each surgeon should be increased, suggested four ways by which this might be achieved: developing standards for workloads, limiting operations with a CRV greater than 4.0 to board-certified surgeons, reducing the number of trainees, and enforcing strict guidelines for credentialing of surgeons by hospital boards. With the exception of some scattered reduction in medical student intake and numbers of training programs, there has been no thrust to achieve these goals. Any effect of the restriction on government funding for GME will not be felt for some time. However, in the United States, because of oversupply and the medical-legal situation, increasing difficulty is being encountered in obtaining surgical privileges without board certification.

Various public health measures have diminished the number of opportunities for surgical operation. These include the use of iodinized salt to reduce greatly the incidence of colloid goiter and the introduction of poliomyelitis vaccine, which eliminated that most common cause of orthopedic deformities requiring corrective operations. Heart disease and stroke have been reduced sharply since 1968, concomitant with secular trends in diet, the treatment of hypertension, the decline in cigarette smoking, and the effect of penicillin on rheumatic heart disease. The use of aspirin prophylaxis alone may be expected to cut significantly the occurrence of stroke after transient cerebral ischemic attacks from carotid atheroma.[8] However, this is the age of ageing, and the increasing proportion of the aged in our population will raise the need for these and other operations more common in the elderly.

Changing surgical concepts have also served to diminish the gravity of operations for cancer of the breast and cancer of the rectum. The Halsted mastectomy and the Miles operation for rectal tumors have been much less commonly performed, and the virtual abolition of routine tonsillectomy as a childhood operation has been traceable both to antibiotics and to changing surgical attitudes.

Randomized, controlled clinical trials are assuming an increasing role in assessment of surgical treatment because historic comparisons are invalid. There may still be debate over the degree of benefit in such complex projects as the coronary bypass studies. However, it is unquestionable that dramatic relief of anginal symptoms occurs and there is clear prolongation of life in left main stem coronary disease or triple vessel disease with impaired ventricular function.

There have been only two randomized clinical trials of carotid endarterectomy, but neither addressed adequately the benefit or lack of benefit of the procedure. Whisnant's careful review of the literature concluded that carotid endarterectomy may be of value provided the procedures are performed with a sufficiently low complication rate.[9] The postoperative mortality/stroke morbidity rate would probably have to be less than 1% to effect a 50% reduction in stroke at 5 years of follow-up. Even the best published surgical results probably have produced only about a 33% reduction in stroke in 5 years. If, as he suggests, the overall combined mortality and stroke morbidity rate is probably between 6 and 10%, then it is possible that the net effect of carotid endarterectomy is unfavorable. In that about 140,000 carotid endarterectomies were done last year in the United States at great expense, it seems, therefore, that further carefully controlled clinical trial is warranted to determine the subgroups most likely to benefit.

Recently, extra- to intracranial bypass using the superficial temporal anastomosis to the middle cerebral artery was not shown to be of benefit over best medical management overall or in any of the many special subgroups examined, regardless of the abundance of the new perfusion.[10] This was true even for severe middle cerebral artery disease and even in the prevention of a subsequent infarction in the same hemisphere. That this attractive operation, a technically demanding microvascular procedure and which can undoubtedly supply the middle cerebral artery circulation,[11] did not hold its promise for stroke prevention was startling to the neurosurgical world. Most major neurosurgical units had developed small microvascular suture laboratories for training and practice in anticipation of an ever expanding field. With a patency rate over 95%, even in vessels under 1 mm in diameter, the operative morbidity rate in humans was reduced to little more than 3–4% in many units. Many surgeons had embraced the procedure as a special interest and a major time commitment. Now few are performed because of medical-legal concerns for adverse outcome, and most third parties have restrictions on reimbursement for the procedure. Why additional blood flow was not important in the face of apparent hemodynamic insufficiency beyond atheromatous stenosis is still not understood, but it may be that thromboembolism rather than reduced flow is the more important reason. Even so, some neurosurgeons have not accepted the results of the study completely, believing that there must be some groups of patients that should benefit, either in the prevention of stroke or in improvement of brain function from increased perfusion of marginally ischemic regions. The burden of proof looms large for the numbers are likely to be small if existent. If the transiently ischemic brain had an incapacitating headache as a part of its syndrome, akin to the heart's angina, then the intracranial bypass procedure might still flourish.

Pharmacology

The story of pharmacology in surgery in the last four decades is truly remarkable. Beginning with penicillin and the abatement of surgery for sepsis, we have witnessed the unforgettable transformation in outlook for the tuberculous patient after the introduction of streptomyocin. There followed the psychotropic drugs that eliminated the mutilating prefrontal lobotomy. Steroid replacement made possible the radical surgery for pituitary and other suprasellar lesions. Immunosuppressive drugs, particularly cyclosporin A, have improved immeasurably the success of transplant surgery. Adjunctive chemotherapy, while still palliative after most tumor surgery, has allowed, in the case of primary bone sarcoma, limb salvage procedures after wide local resection of the tumor with 5–10-year survival rates of at least 30–40%.

Other discoveries in pharmacology, including the radiopharmaceutical I-131 for Graves disease, have eliminated the need for surgical treatment in many disease states. Gone are the days of Pemberton who in one morning performed 19 thyroidectomies.[12] At that time, 3000 thyroidectomies were done annually at the Mayo Clinic; it declined to 1000 per year in the 1960s and now numbers about 300.[13]

Gastrectomy for peptic ulceration, formerly a commonly used method of treatment, is now performed so rarely that in some units there is concern about the number of cases needed to train residents in its technique. This procedure once separated experienced surgeons from the occasional operator, but in a recent survey of Canadian surgeons in smaller communities, gastric operations were last on their lists of the ten procedures most commonly performed.[14] Surgery for hypertension disappeared with sympathetic receptor blockade. Hormonal therapy is reducing the use of hysterectomy for dysfunctional uterine bleeding. Many neuroendocrinologists use bromokryptine for primary control of pituitary prolactinomas, and new drugs show promise for managing successfully the adenomas responsible for Cushing's disease and acromegaly. The classic Spiller-Frazier operation for tic doloreux is no longer performed, replaced by the drug carbamazepine in most instances. In refractory cases, percutaneous needle sensory rhizolysis by electrolysis or glycerol is used especially in the elderly, but posterior fossa microvascular decompression of the sensory root is gaining favor for those who will tolerate this higher-risk procedure. Open cordotomy for cancer pain has been replaced by percutaneous injection techniques. Even this is on the wane because of epidural narcotic infusion.

The decline of stereotactic intracranial surgery was directly related to the introduction of L-dopa for Parkinson's disease. This operative technique still has limited use for certain tremors and for insertion of electrodes for deep ganglionic stimulation in intractable pain syndromes. However, with CT guidance, its use is burgeoning again for tumor biopsy and computer planned isotope insertion. There are glimpses of horizons for stereotactic implant of drug pumps or even neurotransmitter-secreting fetal tissues into deprived brain regions.[15,16] These are the opening vistas for surgical therapy, despite the losses to pharmacologic management.

Technology

In addition to the major influence of social change and pharmacologic advances, we are seeing an unprecedented impact of technology on surgery. This impact shows itself in the monitoring of patient care in and out of the operating room, in diagnostic imaging, and in newer therapies.

Physiologic monitoring of the critical aspects of bodily function is now a daily routine. This practice has had a remarkable influence on the scope and safety of surgery for major injury and illness in both the operating room and the intensive care unit. It is part of the biologic revolution in surgery in the last four decades. Near instant recognition of trouble is available and corrective measures can be applied early and with precision.

Benefits from technology in surgical therapeutics have had a profound influence on every surgical specialty. The dialysis machine extended the field of kidney transplantation. Gibbon's development of a heart-lung machine launched the epoch of modern cardiac surgery. Cardiopulmonary bypass for both open and closed heart surgery is now one of the most common operative procedures in many large hospitals. Electrocardiographic mapping has made precise surgical ablations possible for reversal of certain arrhythmias.

Charnley's introduction of an artificial hip joint changed the face of orthopedic joint surgery. Joint replacement now constitutes a significant portion of orthopedics with at least 100,000 artificial hips implanted annually in the United States. The development of modern prosthetics is impressive; their daily implantation by most surgical specialties has vastly expanded the benefits of reconstructive surgery.

The operating microscope opened a new world for surgeons devoted to the ear, eye, and brain. More recently those specialists involved in reconstructive microvascular surgery have changed dramatically the extent of tissue transplants and limb reimplantations. A vast increase in the scope and precision of surgery has emerged with the greatly magnified vision and superb illumination associated with new microinstruments.

Even suturing has been changed. The use of needle and thread has been the hallmark of the surgeon for centuries and nowhere more so in the last century than for alimentary surgeons in gut anastomosis. Traditional emphasis on the precision with which the sutures were placed was vital to success after a low anterior resection of the rectum as well as for the more accessible anastomoses in the colon, duodenum, and stomach. Now the stapling machine performs this task with greater efficiency and increased speed. Young surgeons do not seem to mind this change and look upon the stapler as a new surgical art form.

However, there is another side to the technology story in the actual or potential displacement of classical surgical procedures to nonsurgical specialties such as radiology, cardiology, and gastroenterology. This is another form of fragmentation, derived chiefly from advances in fiberoptic endoscopy and imaging for guidance of needles, catheters, and endovascular balloons, and new uses of focused high energy. The disciplines most affected are general surgery, neurosurgery, and cardiovascular surgery and, to a lesser degree, urology.

The development of fiberoptics has revolutionized endoscopy for diagnosis and treatment of many lesions of hollow viscera and joints. Sclerosis of bleeding varices *via* esophagoscopy is replacing most portocaval shunts and endoscopic retrograde cholangiopancreatography (ERCP) of the common duct with stone visualization and removal is making occasional most common duct surgery. In the large bowel, endoscopic polypectomy is replacing laparotomy as is coagulation of bleeding sites. Developments in arthroscopy have led to endoscopic joint surgery, most particularly in replacing open surgery for most meniscal lesions of the knee joint and even for cruciate auto- or allografts. Probably because of their rarity, there has been little enthusiasm for ventriculoscopy for lateral and third ventricle brain lesions despite the clear spinal fluid medium, although there has been some resurgence of third ventriculostomy by this route for noncommunicating hydrocephalus.

Interventional or surgical radiology is expanding rapidly. The techniques of surgical radiology developed from a combination of two different facets of diagnostic radiology. First was the ability to image in different planes with great accuracy using ultrasound, CT, and now magnetic resonance imaging (MRI), the latter soon to be in three dimensions. With this precise guidance of needles, trocars, and catheters, its use for biopsy and other manipulative techniques followed. Secondly was the development of the Seldinger arteriographic technique in navigating the major arterial streams with a catheter. To this, the idea of Fogarty et al. of an inflatable balloon-tipped catheter[17] was modified so that the distended balloon could be detached as a stationary embolus[18] and balloons calibrated to leak at their tips after occlusive distension could be used for superselective angiography or injection of a rapidly polymerizing plastic for local embolization.

Combinations and extension of these techniques have led to treatments that are generally less invasive than comparable surgery. There are four general groups of radiologic procedures: biopsy and abscess drainage, biliary and renal catheterization and manipulation, angioplasty, and embolization. A few isolated techniques do not fit easily into categorization: selective infusions, filter placement, and foreign body removal, mostly iatrogenic.

The old surgical adage "pus somewhere, pus nowhere, pus under the diaphram" no longer pertains with modern imaging. The urgent laparotomy for abscess localization and drainage in the abdomen or thorax is unusual and these emergencies are treated primarily percutaneously by radiologists, the cross-sectional imaging of CT and ultrasound ensuring the safety of the method. Similarly, pancreatic pseudocysts are now treated primarily by percutaneous drainage. In selected cases of lumbar disc disease, translumbar needle chymopapain discolysis is still offered as an alternative to the open surgical procedure, even by radiologists.[19]

Both biliary and renal tracts can be catheterized percutaneously as well as endoscopically. By both routes, various adjunctive techniques are available for stenting, stone removal, electrocutting, or dilatation of strictures. Selection of a percutaneous or endoscopic approach can be affected by the site and type of the lesion, clinical condition of the patient, availability of expert personnel, and may be used alone or in combination. But there have been pleas from surgeons to physicians that, in stenting malignant biliary obstruction transhepatically or by duodenal endoscopy, they should not ignore those strictures that may be amenable to surgical cure by exploration.[20]

Further advances in other areas may render some percutaneous therapy obsolete; electrohydrolic "shock wave" lithotripsy will probably replace percutaneous renal stone removal in about 80% of patients.

Investigations with new percutaneous techniques include metal memory wire stenting of aneurysms,[21] pulmonary artery thrombectomy,[22] islet cell infusion transplantation into the portal vein,[23] treatment of gall bladder disease through drainage techniques,[24] lumbar and thoracic discectomy,[25] and transvenous electrical ablations for supraventricular and ventricular arrhythmias.[26] Remarkably, there have been some experimental attempts with transmitting and nontransmitting laser probes to vaporize, endoarterially, stenosing atheromata of major vessels, even in coronary arteries.[27]

Angioplasty and embolization comprise the endovascular therapeutic side of radiology. Angioplasty has quickly become an accepted treatment for stenosis in peripheral and renal arteries, replacing most endarterectomy and bypass procedures, except for lengthy lesions. Dotter and Judkins[28] originally used a Bougie-type catheter in leg arteries through an arteriotomy but the distensible balloon on a double-lumen catheter developed by Gruntzig and Hopff[29] and introduced percutaneously allows wire guidance and even perfusion beyond. Angioplasty for coronary artery stenosis is receiving an ever widening acceptance such that last year more than 100,000 procedures were done in the United States, even multiple stenoses in the same patient.[30] This is up from the 12,000 done in 1982, an explosive growth of this cardiological alternative to bypass surgery. Acceptance of angioplasty in the carotid and intracranial vessels has lagged because of concern about downstream embolic effects from the detritus and the brief interval to infarction if a dissection or thrombosis occurs. However, its use is increasing for atheromatous stenosis in the cervical carotid and vertebral arteries.[31] Intracranially, four severe incapacitating basilar artery stenoses were submitted to angioplasty but there were two deaths from thrombosis or rupture of the artery.[32] Most recent is the emergence of balloon valvuloplasty for dilatation of calcific aortic and mitral stenosis, apparently with very low morbidity.[33] The balloon technique has even been used transvenously to create intrahepatic portosystemic shunts in a nonoperative approach to life-threatening variceal bleeding.[34]

Throughout the story of surgery is the control of arterial bleeding by an open surgical procedure, in the beginning for peripheral trauma but expanding gradually for arterial rupture in the course of injury or disease in all body cavities and viscera in the last century.

To my knowledge, the first planned use of an artificial embolus to control an arterial rupture was that of Brooks of Nashville in 1931, when for a traumatic carotid cavernous fistula he inserted a piece of muscle into the carotid artery in the neck, relying on the high flow to carry it to and maintain it in the fistulous orifice.[35] Later, Luessenhop and Spence introduced another form of blind embolization for AVMs in the brain.[36] Plastic beads of varying sizes were placed into a carotid arteriotomy, again with reliance on the sump effect to carry them to the enlarged feeding arteries and the nidus.

Modern imaging and catheter techniques have expanded the potential of embolization to all arterial systems with greater accuracy and safety. In little more than a decade, emergency celiotomy and thoracotomy for massive gastrointestinal, bronchial, or traumatic retroperitoneal bleeding are on the wane. Transfemoral superselective angiography will often delineate the site of bleeding, and particulate embolization through the same catheter can be used for occlusion of the bleeding vessel. Embolization of extremely vascular tumors can be useful for palliation or as a preoperative measure to ease the surgeon's task.

Arteriovenous fistulae, whether traumatic or congenital, are most common in the central nervous system and had to be treated by Hunterian proximal arterial occlusion or trapping, typically by sacrifice of the internal carotid artery for traumatic carotid cavernous fistula, with its risk of stroke. Detached balloon(s) in or just beyond the fistula in the varix have replaced the surgical techniques while preserving the carotid in the majority of cases.[37] It is now also the preferred method of occlusion of the internal carotid for other reasons, especially for inoperable giant aneurysms on that artery.[38] While avoiding a surgical procedure, it also lessens the dead space from which thromboembolism may arise.

Stirred by Serbinenko's balloon detachments in two intracranial aneurysms in 1974, there is now a gradually increasing use of this method for these aneurysms, especially in Russia,[39] but emerging in Europe, North America, and Japan.[40] There are many problems that seem unlikely to be overcome easily; the various geometries of aneurysms and their origins, their fragility, and the lack of direct control of either the vehicle or the embolic material or aneurysm rupture. However, the technology is at an early stage and is likely to be improved for completeness of the obliteration of the sac and its safety.

Large AVMs, again most common in the brain, remain one of the major neurosurgical challenges for safe complete removal. Kerber's further development of Dotter's calibrated leak balloon allowed not only superselective angiography of these formidable lesions, but the possibility of injecting a rapidly polymerizing plastic into the nidus through the large feeding arteries. This brain arterial navigation with catheters has reached remarkable proportions. Currently, aided by the high flow, even feeders under 2 mm may be cannulated. Unfortunately, this form of embolization is rarely complete and there have been a few serious complications such as rupture of the artery or AVM or cerebral infarction. However, catheter technology is improving and a search for better perfusates has begun.

To add to this is the radiation story, for it was little known until recently that x-radiation had an effect on brain AVMs.[41] Now highly focused forms of radiation using gamma, electrons, or the Bragg peak of protons are being used on AVMs. Called "radio surgery," it is effective for small lesions but there is little discernible effect on large AVMs. However, it is not inconceivable that neurosurgeons will see little of AVMs in the future: the small ones could be irradiated. For the large lesions, interventional and therapeutic radiologists could combine their methods, embolizing them to the extent possible and submitting the remaining smaller nidus to irradiation to complete the obliteration.

Radio surgery alone has also been shown to produce remission in Cushing's disease from pituitary microadenoma in over 85% of cases, and about 50% of acoustic neuromas are reduced in size.[42]

The art and science of surgery have always been in a state of change as we strive to develop the therapy that is best for the surgical patient, even though it may mean a reduction in the opportunity for operative management. This survey of 40 years of change in surgery under the impact of general, pharmacological, and technological influences should not be viewed as a litany of dismay but more as a record of triumph by adapting to these various changes.

No surgeon should be concerned about the loss of a surgical procedure to a drug or to various forms of focused high energy if these alternatives are safer and more effective. However, physicians untrained in the handling of living tissues with instruments have shown a keen interest in involving themselves with endoscopic or percutaneous instrumental therapy for lesions in the body cavities and in the alimentary, biliary, renal, and vascular systems. These new surgical manipulators—I will not call them surgeons—may have emerged because they are the gate-keepers for gastroenterology and vascular disease. The radiologists, already skilled in percutaneous arterial catheter guidance for positive contrast diagnosis, simply injected the embolic material or added balloons to their catheters, a technology that had been developed by surgeons. On the other hand, most general surgeons, vascular surgeons, and neurosurgeons have not pursued these innovations probably because they were misjudged as minor in scope and in technical demands, as well as consuming time better devoted to "cutting" surgery. In addition, there was the barrier to the use of the appropriate x-ray machines that require professional radiological guidance and represent a massive capital investment.

In comment on the surrender of postoperative thoracic surgical care to the intensivist, Magovern continued as an aside: "Indeed, one suspects that if we had kept our focus broader than the operating room, we would not be losing pacemakers to the cardiologist, needle aspiration biopsy to the radiologist and endoscopy to the pulmonologist."[43] In Canada, because of larger surgical workloads and government restrictions on hospital facilities, there is little incentive for surgeons to become involved with these new technologies. However, cardiologists saw the potential and have kept most coronary angioplasty away from the radiologists. Most alimentary surgeons do some of the endoscopic large bowel procedures but only a few have learned ERCP and biliary tract manipulation for stone or stenting, which was developed in the early 1970s and widely used in West Germany and Japan.

A few neurosurgeons are still involved with stereotactic procedures using the new imaging in the brain and for needle placement for ablative procedures directed against trigeminal and body pain. In Japan and at least in Moscow and Kiev, neurosurgeons continue to be in charge of cerebral endovascular procedures, but I know of none in North America or Europe so engaged. The applications from North Americans for training in these techniques in our radiological unit come not from surgeons but from physicians.

Is the disinterest of North American surgeons in involvement with these new interventions using modern imaging and now done by physicians a mistake? I do not deny the physician's knowledge of the physics and hazards of imaging or their manipulative skills in guiding needles and catheters. I am concerned, however, by their lack of training in surgical handling of tissues and the absence of detailed knowledge of surgical disease states and their intimate pathology that is best acquired over long years of training and experience. I suspect most radiologists know aneurysms and AVMs only as shadows on an x-ray film or a television screen and have not seen their infinite variety, complexity, and fragility as exposed at craniotomy or know their morbidity.

It can only be surmised how these new technical developments will evolve, but it is reasonable to predict a burgeoning in experimentation and a diffusion of their use. Whereas now these techniques are used only by a few skilled physicians and radiologists, the potential volume of work is enormous, particularly if coronary and carotid angioplasty can be made safe and effective. If the need materializes, the replication of "invasive" radiologists by preceptorship training may well become exponential so that surgical radiology will be available in at least most large hospitals within a few years. One can foresee too that vascular surgeons and neurosurgeons and their operating rooms would have to remain on standby to deal with the complications, just as cardiac surgeons now do for coronary angioplasty. Further, the production of large numbers of these physician-operators will inevitably lead to problems associated with dilution of judgement and experience.

Three possibilities may be envisioned for the evolution of invasive radiology in North America. The first would be to continue to admit patients on the surgical service and have the surgeon share responsibility with the radiologist as now occurs in most units. In this setting, the radiologist will profit from the accumulated surgical knowledge of the disorder and its patterns, which are invaluable in the decision process, in avoidance of technical pitfalls and in perceptive follow-up.

The second option would be the development of special radiological units with bed allotment and admitting privileges; these would be staffed by radiologists and their residents, as has occurred at Johns Hopkins.[44] Such an arrangement risks development of these techniques in isolation from the mainstream of surgery, relying, as in the case of limited license practitioners, on consultation for general and emergency medical and surgical care. Some radiologists believe this is the most appropriate arrangement for their new specialty. They have stated that "this broadens the referral base because community physicians will refer patients for treatment such as peripheral angioplasty without losing control of the patients to a clinical colleague on whom they must depend to obtain our consultation."[44] Further, there is chronic frustration among many radiologists who believe that self interest by some referring surgeons plays too big a role in selection of an appropriate therapy. This has led, in the radiologists' view, to gross underutilization of some newer procedures.[45] They even suggest "a radiological second opinion" as an option before patients undergo certain elective surgical procedures.[46] Radiologists fancy that this might result in improved or equivalent care at less cost and lower morbidity.

A third possibility is the emergence of a new type of practitioner, one with training in both surgery and radiology at a resident level and certification in one or other specialty. Such practitioners might be acceptable for work in either department. Subspecialty recognition of interventional radiology in the form of "added qualification" is being considered by the American Board of Radiology.[46] Their proposed revision of special requirements states it is expected that each resident will have experience in interventional procedures, angioplasty, embolization and infusion procedures, and percutaneous introduction techniques in the biliary and genitourinary systems.

McLuhan's electric age is upon us; surgeons might well regard it as the age of imaging. I have recently developed the conviction, that before it is too late, some young surgeons should become involved with the new imaging and the developing endoscopic techniques, especially in vascular surgery. At least in the beginning, the development of such young surgeons should be done in partnership with their radiological colleagues because it will be necessary to learn many important skills. In this way, development would be complementary rather than competitive between specialty fields. Few surgeons may have access to machines where the cost of imaging can be duplicated with appropriate technical help in the way some cardiologists have managed.

The same may be said for most other aspects of surgical radiology, at least until it can be seen whether or not surgeons can carry further these new and different surgical adventures. In the past, surgeons have shown no lack of ingenuity in technical matters. There should be no thought that these percutaneous techniques are beneath the dignity of a surgeon. I recall the extended discussion in the councils of ophthalmology and in the Board of Regents of the American College of Surgeons as to whether an ophthalmologist who restricted his practice to laser surgery was truly a surgeon; it was decided in the affirmative. Similarly, ultramicrosurgery, about which some speculate, would surely have to be done with machines.

Surgical horizons are broad; they beckon for all the surgical specialties. However, greater changes in the face of surgery will probably come from pharmacology, immunology, and technology. Advances are usually unanticipated. They often come not from intraspecialty expertise, but from other fields of endeavor. The enquiring investigative surgeon must keep abreast of these developments in fundamental science and new technology and become involved with their application to surgical disease. Young surgeons should not shy away from the often incredible complexity of newer basic developments. Immunology promises to marshal our inner defenses against infection and malignancy. In neuroscience the rapidly advancing story of the neurotransmitters mediating central nervous system effects may result in a new field of "implantation." Mann believes that we can expect to see intense effort being made in research fields related to cardiovascular disease and cancer, which are now by far the killing diseases of the mature and aged.[47] "We must surely expect to see sacrifices made in order to drive our knowledge of these diseases nearer to the point in their molecular biology at which rational therapeutics can evolve meaningful preventatives and remedies. This effort must be expected to preoccupy the next few decades, for we have already reached the point at which our knowledge of the oncogenes is likely, within the next few years, to be applied to the management of cancer." "Most startling of all, and within not much more than a decade, it has become fairly clear that genetic engineering and related technology represents the biggest single advance in the lif sciences since the advent of the antibiotics." What effect these genetically engineered vaccines and monoclona antibodies and other unborn technology will have on th surgical craft is unclear, but effect there will be, if only as with the antibiotics, to extend even further the scope and depth of surgery.

I close with a comment I have made mostly to neurosurgeons, but it applies to all the surgical sciences where so much remains unknown: that academic surgeons should exploit one great advantage they possess over the basic scientist in having exposed daily some organ, lesion, or other structure for study. That must be why Wilder Penfield said "The opportunity to learn walks with any surgeon who enters the operating room with questions on his mind."

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Pigment Gallstones Form as a Composite of Bacterial Microcolonies and Pigment Solids

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Although previous studies have suggested that bacteria may contribute to pigment gallstone formation, the current experiments provide evidence that bacteria have a central role in this process. The studies included scanning electron microscopy (SEM) of gallstones, measurements of bacterial adherence to gallstones *in vitro*, and determination of glycocalyx elaboration by biliary bacteria. Gallstones from 85 patients were studied under SEM. Twenty-five (78%) of 32 pigment stones had evidence of bacterial microcolonies throughout the interior of the stones. Bacteria were absent from the interior of all 35 cholesterol stones studied. Composite stones (stones with separate pigment and cholesterol portions) showed evidence of bacteria within the pigment portions in 14 (78%) of 18 cases. Biliary bacteria adhered to the surface of pigment gallstones *in vitro* in 35 (90%) of 39 cases, compared with three (8%) of 39 cholesterol stones. Glycocalyx was elaborated by bacteria isolated from nine (82%) of 11 patients with either pigment or composite gallstones. One (33%) of three bacterial species from patients with cholesterol gallstone disease produced glycocalyx. These studies indicate that most pigment gallstones obtained from patients in Western cultures form as a composite of bacteria, bacterial glycocalyx, and pigment solids. Bacteria were found in the majority of black as well as brown pigment stones. These findings serve as the basis of a new theory of pigment stone formation in which bacteria and glycocalyx are postulated to be responsible for the precipitation and subsequent agglomeration of bilirubin pigment. These results also suggest that sepsis is more common in pigment gallstone disease because the stones can serve as a sanctuary for bacteria.

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PREVIOUS STUDIES HAVE SUGGESTED that bacteria may have a special role in the pathogenesis and clinical manifestations of pigment gallstone disease. For example, we[1] and others[2-4] have shown that infectious complications are much more common in patients with pigment than with cholesterol gallstone disease. However, the role that bacteria play in the formation of pigment gallstones remains incompletely defined.

Maki postulated that bacteria, by secreting β-glucuronidase, could deconjugate bilirubin diglucuronide, which would then precipitate as calcium bilirubinate.[5-7] He believed that the precipitate was probably cemented together to form macroscopic stones by biliary anionic glycoproteins.

Since Maki's theory was presented in 1966, many experiments have been performed to test its tenets. Currently, the generally accepted view is that pigment gallstones can be divided into two types.[8-11] The first type of pigment gallstone is the brown, earthy stone, which is said to occur principally in the Orient. It consists mainly of calcium bilirubinate and calcium palmitate and is believed to develop as the result of infection and biliary stasis. These brown pigment stones typically originate in the common bile duct in preference to the gallbladder. The second type is the black pigment stone, which usually forms in the gallbladder, contains bilirubin polymers in addition to calcium bilirubinate, and is believed to be unrelated to infection. With few exceptions, patients in Western countries who have pigment gallstones have been considered to belong in this second category.[11] The pathogenesis of black pigment stones involves hemolysis in some cases, but in most cases the cause is unknown. Thus, Maki's theory about the origin of pigment stones has been generally accepted for brown stones found in patients in the Orient, but not for the majority of stones found in patients in Western countries.

Since Maki implicated anionic glycoproteins in pigment stone formation, little work has been done to identify specifically how pigment solids become com-

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pacted into stones.[12] Recently, bacteria have been shown to secrete exopolymers, most often referred to as glycocalyx, which are associated with bacterial microcolony formation on foreign bodies.[13-18] This substance, an anionic glycoprotein, is believed to contribute to the ability of bacteria to adhere to surfaces and to resist the effects of antibiotics, phagocytes, antibodies, and surfactants. Glycocalyx can also serve as an ion exchange resin for nutrients needed by the proliferating bacterial colony.

In the current study we examined some of these ideas and have made new observations on the composition of pigment gallstones. The following experiments were performed: a study of the morphology of gallstones using scanning electron microscopy (SEM); measurements of the affinity of bacteria for the surfaces of pigment and cholesterol gallstones *in vitro;* and a determination of the ability of biliary bacteria to elaborate glycocalyx. The results provide substantial new evidence that implicates bacteria in the formation of most pigment stones encountered in Western cultures.

Methods

Morphology of Gallstones

Two categories of gallstones were studied: fresh stones from 32 patients and previously air-dried stones from 53 patients. Only five patients, all Filipinos, had lived in the Orient for an extended period, but they were not recent immigrants. The stones were classified according to their source (gallbladder or common bile duct), gross visual appearance, and composition (Table 1).

The fresh stones were collected and studied prospectively between October 1985 and April 1987. The 32 patients ranged in age from 19 to 96 years and included 23 men and nine women. The ethnic distribution was 21 white patients, four black patients, five Filipino patients, one Hispanic patient, and one Chinese patient. Detailed clinical data were available for all 32 patients.

The air-dried stones were collected between October 1978 and December 1986. This group included gallstones obtained from 15 patients from Essex, England and 38 patients from San Francisco. Clinical data were available on 39 of these patients. The patients ranged in age from 29 to 81 years and included 19 men and 20 women. The ethnic heritage of these patients was as follows: 31 white, one black, five Filipino, one Chinese, and one Malaysian.

The fresh stones were processed immediately after removal from the patients and were not allowed to desiccate. After being photographed, the stones were rinsed in sterile saline and fixed in 5% gluteraldehyde–0.1 M cacodylate buffer at pH 7.0 for 2–10 days, depending on stone size. They were then buffered in 0.1 M cacodylate buffer for at least 1 hour, dehydrated through ascending ethanol concentrations, and critical-point dried. The air-dried stones did not require the above processing. All stones were split and then gold or platinum sputter-coated to 25–40-nm thickness. The surface and interior of each stone was examined under SEM at 10–20 kV using an ISI DS-130 or Cambridge S-150 scanning electron microscope.

TABLE 1. *Classification of Gallstones (106 Stones from 85 Patients)*

Stone	Source	No. of Fresh	No. of Dried	Total
Pigment	GB	8	16	24
	CBD	8	10	18
Cholesterol	GB	10	17	27
	CBD	5	12	17
Composite	GB	5	4	9
	CBD	2	9	11

Bacterial Adherence to Gallstones

The tendency for bacteria to adhere to gallstones was studied using 78 gallstones (39 pigment and 39 cholesterol). The gallstones had previously been allowed to dry and were sterilized for the purpose of this experiment using ethanol or gas sterilization. For each experiment, 1–3 pigment and 1–3 cholesterol stones were individually incubated in identical solutions. The stones were incubated in a 37 C water bath for 1–3 days in a bacterial suspension of 10^7–10^8 CFU/mL with tryptic soy broth (36 stones) or human bile (42 stones). Fifteen species of bacteria isolated from bile were studied: *Escherichia coli* (7), Enterococcus (3), *Klebsiella pneumoniae* (3), *Pseudomonas aeruginosa* (1), and mixed gastrointestinal flora (1). The bile used for the incubation was obtained from seven patients. Two of these patients had bile collected from T-tubes after operation, one patient had bile collected at operation, two patients had neoplastic biliary obstructions with sterile bile, and two patients had infected bile (one had gallstone disease and one had a benign biliary stricture). The biles were sterilized by passage through a 0.45-millipore filter and were plated to confirm their sterility.

After incubation, each stone was rinsed in sterile saline and fixed in 5% gluteraldehyde–0.1 M cacodylate buffer at pH 7.0. The specimens were further rinsed with 0.1 M cacodylate buffer for 1 hour, dehydrated through ascending ethanol concentrations, critical-point dried, and gold or platinum sputter-coated to 25–40-nm thickness. The stones were examined under SEM (ISI DS-130 or Cambridge S-150) at 10–20 kV to determine the presence of bacterial microcolonies adherent to the surface.

Glycocalyx and Biliary Bacteria

The ability of bacteria to elaborate glycocalyx was determined using ruthenium red and PAS staining. Thirty-one species of bacteria were obtained from bile

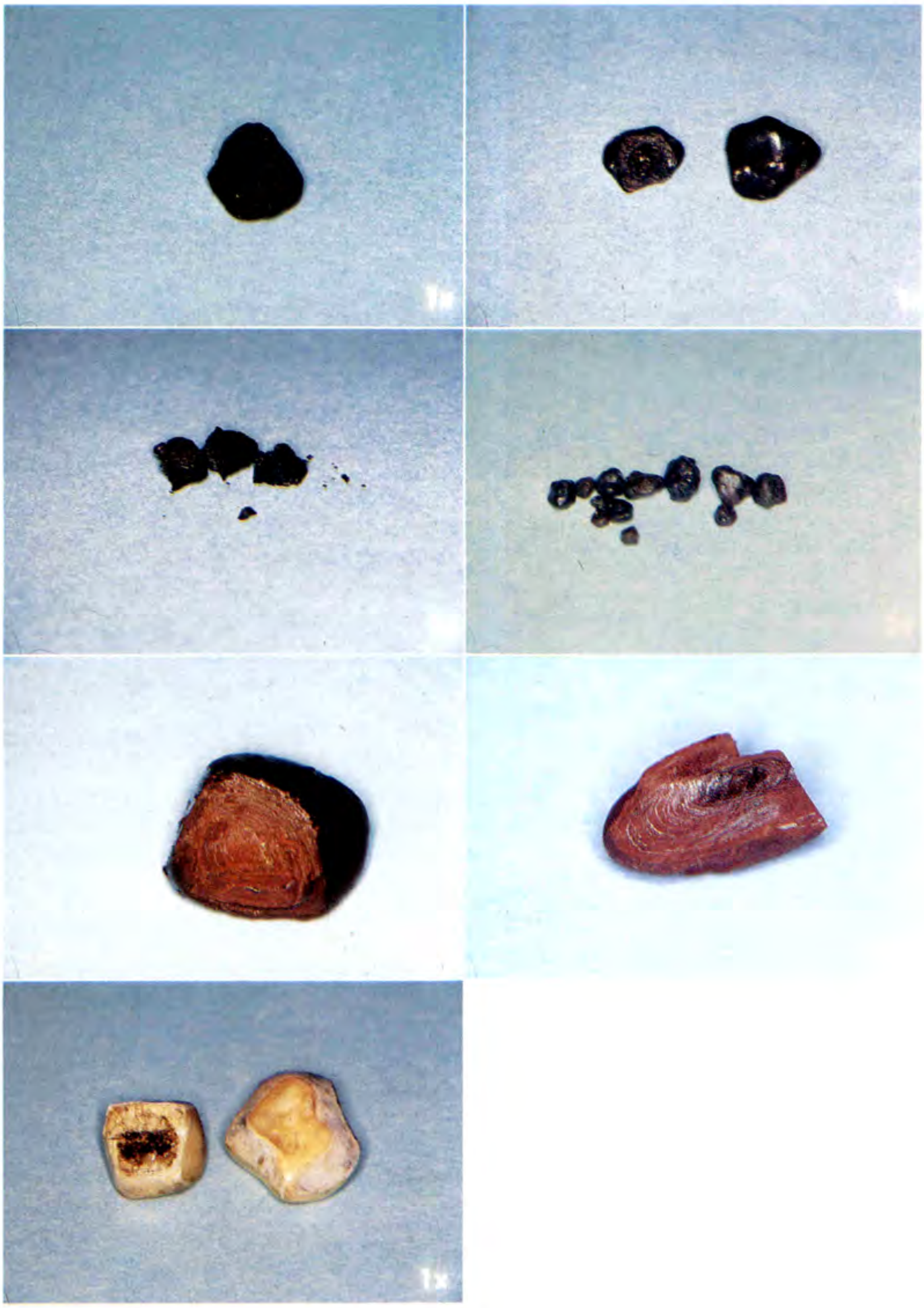
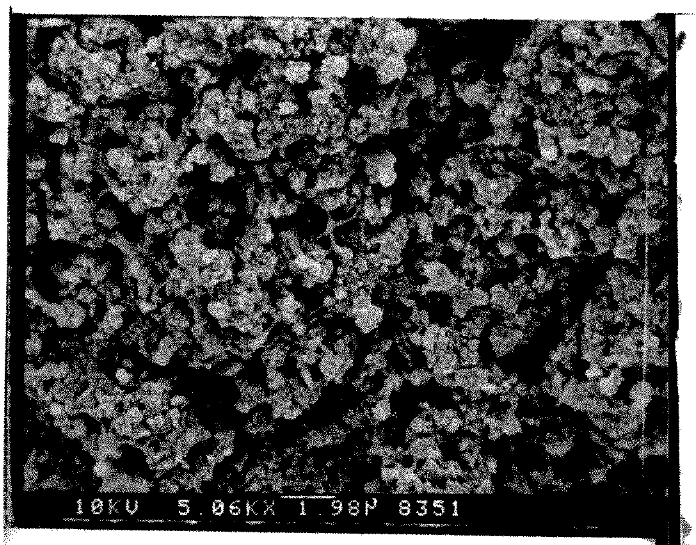


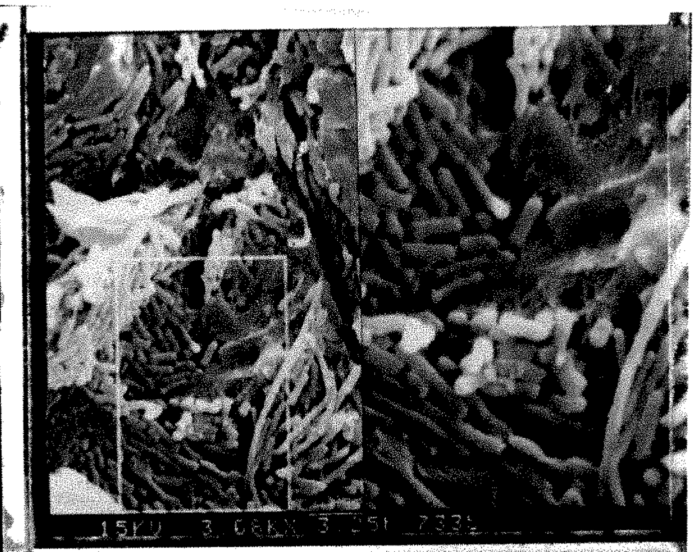
FIG. 1A. *Top row left.* Air-dried black gallbladder pigment stone. FIG. 2A. *Top row right.* Fresh black gallbladder pigment stone. FIG. 3A. *Second row left.* Fresh black common duct stones. FIG. 4A. *Second row right.* Fresh black pigment gallbladder stones from a patient with hemolysis. FIG. 5A. *Third row left.* Air-dried brown pigment gallbladder stone. FIG. 7A. *Third row right.* Air-dried pigment common duct stone. FIG. 8A. *Bottom left.* Typical facetted cholesterol common duct stone.

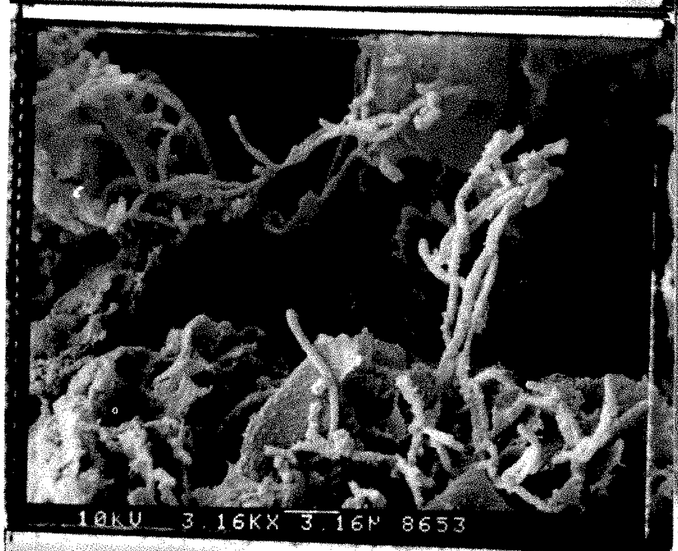
cultures from 14 patients. The species included 11 *E. coli,* four *K. pneumoniae,* two Enterococcus, one *P. aeruginosa,* one *Streptococcus viridans,* one *Proteus mirabilis,* one *Klebsiella oxytoca,* and 10 other gut species that were not specifically identified. Each bacterial isolate was incubated overnight in tryptic soy broth at 37 C. Next, 100-μL aliquots of the bacterial suspensions were placed onto glass slides, air-dried, and gently heat fixed. The slides were stained with ruthenium red as described by Mills et al.[14] or PAS. Glycocalyx elaborated by bacteria was assessed from appropriate background staining under light microscopy.

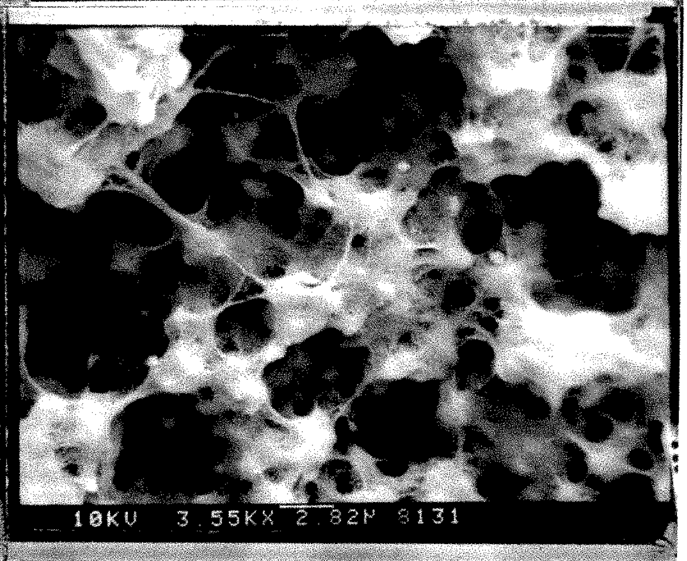
Culture Data

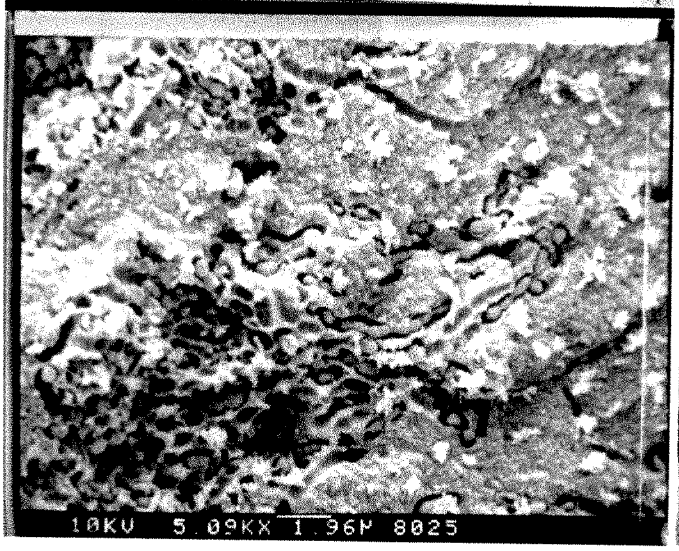
Results of bile cultures obtained from 29 patients during operation were tabulated and compared with











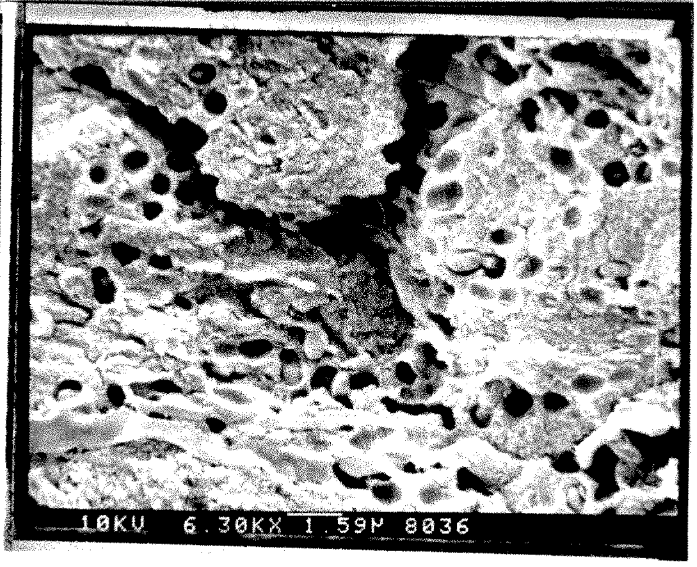


FIG. 1B. *Top left.* SEM shows pigment and no signs of bacteria (original magnification ×5060). FIG. 2B. *Top right.* SEM of stone interior showing numerous bacteria imbedded in pigment solids. (Left panel, original magnification ×3080; right panel, original magnification ×6160). FIG. 3B. *Middle left.* SEM of stone interior showing numerous bacteria and pigment solids (original magnification ×3160). FIG. 4B. *Middle right.* SEM of pigment solids without signs of bacteria (original magnification ×3550). FIG. 5B. *Bottom left.* SEM of stone interior showing bacterial casts, many of which contain bacteria (original magnification ×5090). FIG. 6 *Bottom right.* SEM of the interior of an air-dried pigment common duct stone showing bacterial casts, most of which are empty (original magnification ×6300). When examined in the fresh state, every cast contained a bacterium.

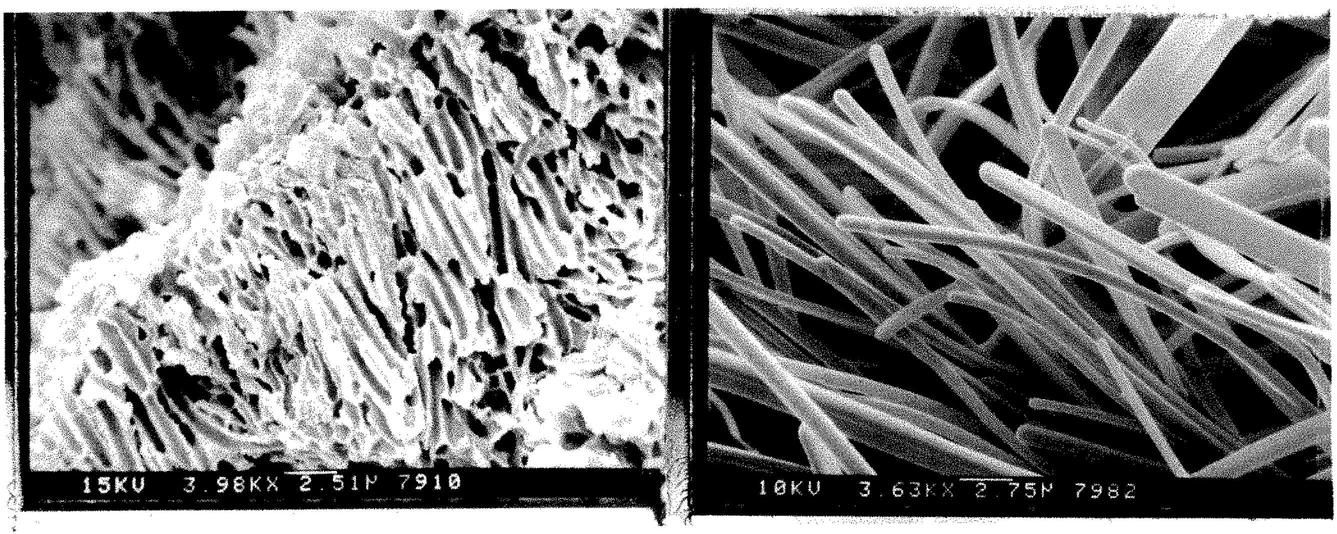


FIG. 7B. *Left.* SEM of the stone interior showing numerous bacterial casts devoid of bacteria (original magnification ×3980). FIG. 8B. *Right.* SEM of the stone interior showing cholesterol crystals and no bacteria or casts (original magnification ×3630).

stone composition, stone source, and SEM findings of the corresponding gallstones.

Results

Morphology of Gallstones

The cholesterol and pigment stones had distinctive appearances both grossly and by SEM. The gross visual estimate of stone composition always conformed with the SEM characteristics of the stone.

Pigment stones. Although the gross appearances of pigment stones from different patients varied, the solid material in these stones looked similar under SEM. The surfaces of pigment gallstones exhibited an amorphous, barren, desert-like landscape. The interior of pigment stones consisted of small (<0.5 μm) granules of varying size and shape studding the field (Figs. 1A and B).

Twelve (92%) of 13 fresh pigment gallstones had bacterial microcolonies on their surface and/or comprising the matrix of the stone (Figs. 2A and B) (Table 2). All stones with bacteria on their surface also had bacteria within their interior. All common duct pigment stones had bacterial microcolonies easily identifiable by SEM (Figs. 3A and B.). The fresh pigment gallstones from only one patient did not demonstrate bacteria (Figs. 4A and B). These were gallbladder stones obtained from a 67-year-old man who had a history of hemolysis due to an aortic valve prosthesis.

TABLE 2. *Relationship of SEM Findings to Type of Gallstone*

Stone	No. of Patients	State	Positive SEM	Comments
Pigment	13	Fresh	12 (92%)	Bacteria and/or casts
Pigment	19	Dried	13 (68%)	Bacteria and/or casts
Cholesterol	12	Fresh	1 (8%)	Bacteria and/or casts
Cholesterol	23	Dried	0	Sterile
Composite	7	Fresh	5 (70%)	Bacteria and/or casts in pigment portion only
Composite	11	Dried	9 (82%)	Bacteria and/or casts in pigment portion only

Both fresh and air-dried pigment stones also exhibited many spaces or troughs in the pigment solid (1–2 μm in diameter and 2–4 μm in length), which occurred in groups (Figs. 5A and B). In the fresh pigment stones, the spaces usually contained bacteria, but bacteria were seen only in dried stones that were studied within 10 months of removal. After 10 months, the cavities were empty. These cavities, which we called "bacterial casts," represent spaces currently or previously occupied by bacteria.

To document that these casts were actually physical impressions of bacteria, fresh stones from two patients were examined serially. The first set (one stone from each patient) was processed and examined immediately, and the second set was processed after being allowed to dry at room temperature for 2 months. Bacteria were present within casts on the first examination in both cases, but 2 months later the casts were entirely empty of bacteria in one patient and only sparsely populated with bacteria in the other (Fig. 6).

Thirteen (68%) of 19 air-dried pigment stones showed bacteria and/or bacterial casts in their interior (Figs. 7A and B). The pigment stones from all eight patients from England, all of whom were white, showed evidence of bacteria. Of the patients whose stones displayed no evidence of bacteria, one had a history of hemolysis due to hereditary spherocytosis. There were no distinguishing features common to the other five patients.

Cholesterol stones. The surfaces and interiors of cholesterol stones showed crystals in oakleaf, needle-like, and slab forms (Figs. 8A and B). The size of these crystals varied, but they always exhibited sharp, squared-off borders and uniformity within a given field.

One (8%) of 12 fresh cholesterol gallstones examined demonstrated bacteria on its surface. This cholesterol stone was obtained from a patient whose bile culture grew Klebsiella, Streptococcus, and Proteus. No bacteria or bacterial casts were present within the interiors of any fresh cholesterol stones. In addition, none of the dried cholesterol stones had evidence of bacteria or bacterial casts.

Composite stones. Composite stones were those that on gross inspection had separate pigment and cholesterol portions. The pigment and cholesterol portions of composite stones could be distinguished under SEM from the characteristic features described above. The composite stones from 18 patients could be separated into four groups: cholesterol stones with a small pigment nucleus (6 patients); a pigment stone with a cholesterol coat (1 patient); cholesterol stones with a pigment coat (4 patients); and onion skin stones with alternating layers of pigment and cholesterol (7 patients).

Bacteria were noted within the pigment centers of two (33%) of six cholesterol stones. Bacteria or bacterial casts were seen within the pigment coats of all four composite stones with cholesterol centers and in the center of the one pigment stone with a cholesterol coat. Bacteria or bacterial casts were evident in the pigment areas of all seven composite onion skin stones. None of the cholesterol portions of the composite stones showed bacteria.

Bacterial Adherence to Gallstones

Of the 78 gallstones that were incubated in various bacterial cultures, microcolonies of bacteria were found adherent to the surfaces of 35 (90%) of the 39 pigment gallstones. This included all the bacterial species studied except *P. aeruginosa*. By contrast, only three (8%) of the 39 cholesterol stones demonstrated sparse microcolonies after incubation with a single species of *E. coli*.

Glycocalyx and Biliary Bacteria

One or more bacterial isolates from 10 (71%) of 14 patients stained positively for glycocalyx: six (80%) of eight bacteria from patients with pigment stones; one (33%) of three bacteria from patients with cholesterol stones; and three (100%) of three bacteria from patients with composite stones. The appearance of the glycocalyx staining could be divided into moderately positive and intensely positive. With one exception, intensely positive glycocalyx stains were seen only with bacterial strains obtained from patients with pigment stones. The patient with cholesterol stones who had intense bacterial staining for glycocalyx was the same patient whose stones had surface bacteria under SEM. Bacterial microcolonies were present within all pigment stones whose corresponding bacterial isolates produced glycocalyx.

Culture Data

Bile cultures grew bacteria in 18 (66%) of 29 patients. Pigment gallstone disease was associated with positive bile cultures in 10 (83%) of 12 cases. All patients with pigment common duct stones had positive cultures. The biles from patients with cholesterol gallstones were infected in four (33%) of 12 cases. Finally, bile associated with composite stones had an 80% incidence of biliary infection.

The stones found by SEM to contain bacteria or bacterial casts in their interior were compared with the results of the bile cultures. All pigment stones recovered from patients with positive bile cultures were found by SEM to contain bacteria, whether the stones were obtained from the gallbladder or the common duct. SEM demonstrated bacterial microcolonies on the surface of the stones from only one of four patients with both cholesterol stones and biliary infection.

The results of bile cultures were available for five patients with composite stones: two were stones with pigment cores and cholesterol shells, and three were stones with cholesterol cores and pigment shells. Bile cultures were positive in four of these cases. SEM demonstrated evidence of bacteria in the pigment portion of each of these five stones, whether the pigment was central or on the surface. Composite stones never demonstrated bacteria in the cholesterol portion of the stone.

Discussion

These experiments show that bacteria are present throughout the interior of most fresh pigment gallstones. No bacteria were seen within cholesterol stones, indicating that the relationship of bacteria to pigment stone disease is specific. The patients from whom the pigment stones were removed were not selected; they represented consecutive cases encountered by the authors over several years. The distribution of pigment and cholesterol stones does not reflect their relative frequency among our patient population, however, because we did not examine stones from all patients with cholesterol gallstone disease. With few exceptions the patients were natives of the country where their surgery was performed (*i.e.*, the United States or England) and only five had lived in the Orient for a prolonged period. Therefore, the stones were representative of the spectrum of pigment gallstone disease that characterizes Western cultures.

Pigment stones allowed to dry for several months often contained no bacteria, but their presence was indelibly recorded by the molds they left behind. Several

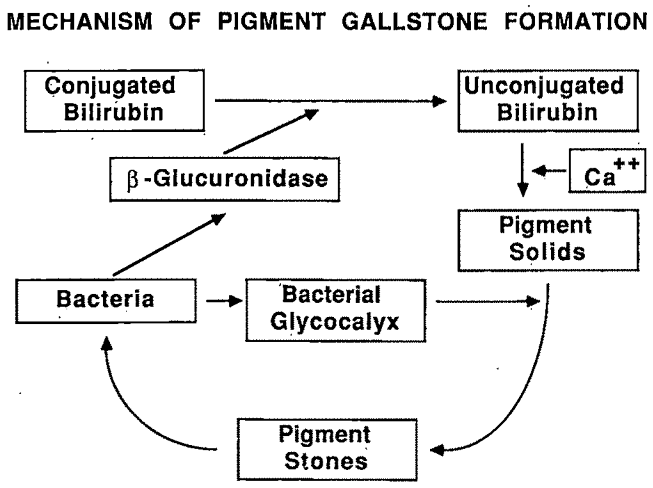


FIG. 9. Proposed mechanism of pigment gallstone formation by bacteria. This theory includes a role for glycocalyx in the development of the stone. Other putative factors discussed in the literature but not directly studied in this experiment have not been included (*e.g.*, inhibitors of β-glucuronidase).

other workers have noted these spaces in pigment stones, but their significance had not been recognized, probably because only dried stones were examined, which contained no bacteria.[10,19–21] We could verify the relationship of bacteria to casts by studying stones serially and noting bacteria when the stones were fresh and their gradual disappearance with time.

The similarity between the SEM appearance of pigment gallstones and that of infectious (struvite) kidney stones is striking.[22,23] These kidney stones also feature bacteria and bacterial casts, and their appearance in some photographs is difficult to distinguish from the pigment gallstones we studied.

A few of our pigment stones had no traces of bacteria. Hemolysis could be implicated as an etiologic factor in two cases, but other etiologic factors were not apparent in the remainder. Therefore, other mechanisms of pigment stone formation remain to be determined. In the composite stones (the stones with distinct pigment and cholesterol portions), bacteria and bacterial casts were present only within the pigment portions of the stones.

The findings of this study call for a revision of current theories concerning the pathogenesis of pigment stones in Western cultures. Although it is accepted that bacteria are involved in the formation of pigment stones in the Orient, this mechanism has been believed to be rare in Western countries.[9,10] The brown "stasis" stones typical of patients in the Orient are said to be uncommon outside that area. When they are encountered, it is believed to be in association with repeated biliary infections and previous biliary surgery. Cetta, for example, demonstrated bacteria by SEM within the stones of two such patients.[3]

We found, however, that bacteria occupied the interior of all kinds of pigment stones, both black and brown. Most of our patients had not had previous biliary surgery and, in general, the clinical severity of their disease was not extraordinary. As suggested by Bernhoft and co-workers,[1] we believe the distinction between black and brown stones has been somewhat overstated in recent literature. Rather than falling neatly into two groups, pigment stones display a spectrum of appearances ranging from the crumbly, milk chocolate, laminated, brown stone at one extreme to the hard, coal black, obsidian-like stone at the other. The pigment stones we studied that contained no bacteria were all of the coal black variety, but those with bacteria spanned the entire spectrum. We have shown also that earthy brown stones are more common in Western countries than has been previously stated, as we found nearly equal numbers of black and brown stones in this and our previous study.[1] Although chemical differences have been detected between black and brown stones,[10] both kinds of stones contain bacteria. Therefore, the differences cannot be explained in terms of bacterial activity.

The *in vitro* experiment demonstrated that biliary bacteria have a special affinity for pigment but not cholesterol solids. Bacterial adherence is usually required before the expression of virulence, and adhesion to a surface has been noted to be the initial step in many bacterial diseases.[24–28] For example, the various *E. coli* sp. responsible for urinary tract infections and gastrointestinal diseases possess adhesins that allow them to adhere specifically to their respective epithelia. Our data suggest a specific adhesin-receptor model by which bacteria attach to pigment solids. Adhesion may be mediated by bacterial glycocalyx, a charged glycoprotein that extends from the bacterial surface and contributes to the ability of bacteria to adhere to other surfaces.[13] The majority of bacteria we isolated from patients with pigment gallstones produced glycocalyx.

There are several ancillary findings of note. One concerns the presence of bacteria within the small pigment center of two cholesterol gallstones. In the past, there was speculation that these dark centers might represent a pigment nidus of crystallization for cholesterol gallstone formation.[29,30] Malet and co-workers,[31] however, found only traces of pigment solids in this type of gallstone, and as a result of their report, the idea fell into disfavor. Although most dark centers of cholesterol stones that we studied by SEM showed cholesterol and no visible pigment, bacteria, or casts, our findings of bacteria and pigment in two stones should revive this possibility.

We have shown that pigment stones form as a composite of bacteria, bacterial glycocalyx, and pigment solids. Maki postulated that bacterial infection can lead to calcium bilirubinate precipitation by the elaboration of the enzyme β-glucuronidase, which deconjugates bilirubin diglucuronide.[5–7] Monoconjugated and unconjugated bilirubin are much less soluble in bile and precipitate as calcium bilirubinate crystals. For macroscopic stone growth, Maki postulated the need for "coagulation factors" that would cement the bilirubinate sediment together. He identified anionic glycoproteins within the matrix of pigment stones by special staining with PAS and Alcian Blue. Similar glycoproteins were also identified in the bile of patients with pigment gallstones.[7] Bacterial glycocalyx is an anionic glycoprotein with the same chemical properties as Maki's coagulation factor. As a polyanionic substance, it also stains with ruthenium red.[14] The elaboration of glycocalyx by bacteria isolated from patients with pigment stones and parallel evidence implicating glycocalyx in the formation of infectious kidney stones[23] suggest that bacterial glycocalyx may be the coagulation factor, but there are other possibilities.[24–28]

Figure 9 illustrates a proposed new theory of pigment gallstone formation. Biliary infection is the initial event. Biliary bacteria produce β-glucuronidase, which deconjugates bilirubin diglucuronide. The bacteria also elaborate glycocalyx, which contributes to the formation of a protected bacterial microcolony on which the pigment coalesces. Glycocalyx, therefore, serves to organize and protect the bacterial microcolony and provide the latticework for pigment deposition. Compared with earlier work, the new elements of this theory are the recognition that: (1) bacteria actually constitute a substantial portion of the stone and are more than just a remote source of β-glucuronidase; (2) bacteria possess specific adhesion properties that are probably instrumental in the creation of the stone; (3) bacteria are responsible for the formation of the majority of black as well as brown stones; and (4) bacteria are primarily responsible for the formation of most of the pigment stones in Western countries as well as in the Orient. In addition to this primary role of bacteria in pigment precipitation and agglomeration, these findings also explain why sepsis is more common in pigment gallstone disease, since the stones serve as a sanctuary that protects the bacteria from endogenous and exogenous antibacterial factors.

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Discussion

DR. ROBERT ZEPPA (Miami, Florida): I would like to congratulate the authors on a beautifully illustrated, well-designed, and elegant study.

I rise only for one question. The techniques you mentioned for staining a glycocalyx are nonspecific and stain all glycoproteins. How do you know that that was not gallbladder or bile duct mucus that you stained in the course of these experiments?

DR. FRANK G. MOODY (Houston, Texas): Dr. Stewart has provided us with a rather intriguing concept and started out by saying that she was going to provide us with proof that bacteria, indeed, play a role in the genesis of such stones.

Lygia and I go a long way back to Utah, and we know each other very well, and we also know what proof is. One could, however, interpret the data in a different way. In fact, she has presented evidence that this probably is the case, and that is that pigment has an affinity for bacteria, and as the pigment agglomerates, it tends to trap the bacteria.

I believe this is an important point for the authors to address because if, indeed, bacteria are the nidus, if you will, for the precipitation of the crystals and their agglomeration, then we should be paying more attention to trying to completely rid the biliary tree of infection.

There is no question that the authors are onto something because we all know if we do not provide for the flow of bile that bacteria indeed do accumulate.

I also am curious as to whether the population that they dealt with in San Francisco (probably not in England, but possibly there also) might not have been from the Orient because it is clear that in the Orient, bacteria seem to play a critical role in the formations of stones.

I would like to bring to the attention of the membership two trials of extracorporeal lithotripsy for stones that will be performed in this country in the next 1.5 years. Those of you, like I, who work with patients with gallstones should watch these trials carefully because it is clear from the studies in Munich that gallstones within the gallbladder as well as in the common duct are going to yield to this type of therapy.

Therefore, I ask Dr. Stewart, or whoever closes, how, indeed, are we going to prevent the reformation of these stones once we remove them with lithotripsy or other nonsurgical methods?

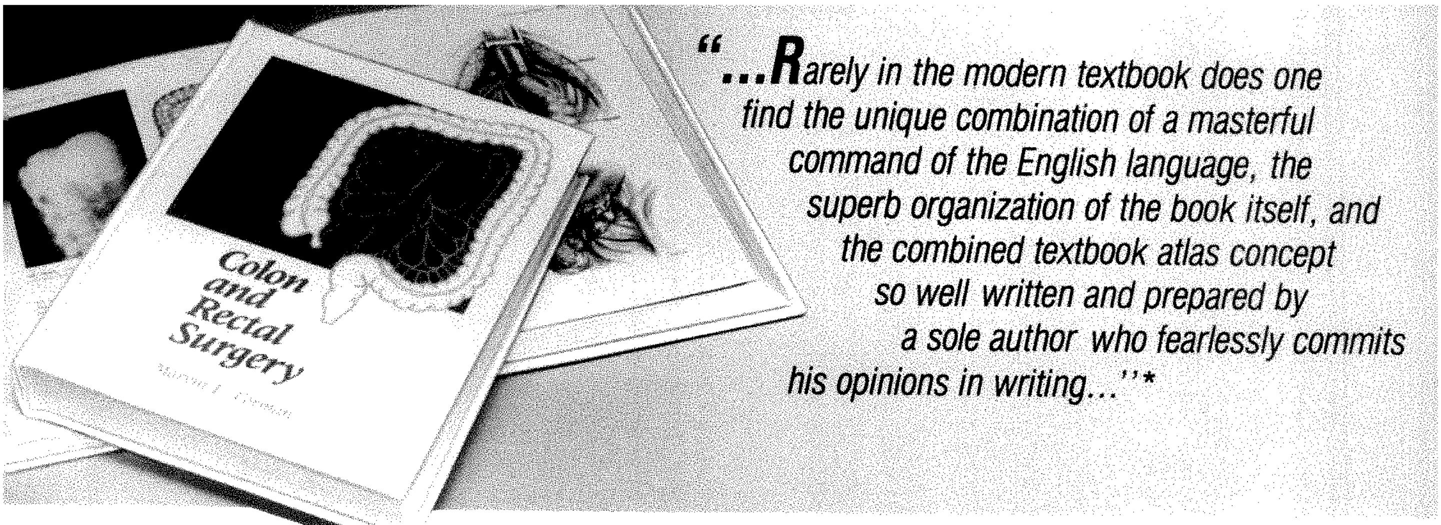
DR. LAWRENCE W. WAY (Closing discussion): I want to thank the discussants for their comments.

In response to Dr. Zeppa's question, staining for glycocalyx was performed on the bacterial isolates, not on the stones. We were interested in knowing whether the bacteria isolated from patients with pigment stones manufactured glycocalyx.

I am not sure that we convinced Dr. Moody. I suppose it is possible that the stones came first and the bacteria second, but that seems unlikely. We were intrigued, for example, by the similarities between the pigment gallstones obtained from our patients and infectious bladder stones. (Slide) This slide illustrates how closely experimentally produced kidney stones (the slide was photographed from an illustration in a report by Takeuchi et al. J Urol 1984; 132:67) resemble gallstones from the common bile duct when examined by scanning electron microscopy. The conditions of the experiment indicate that the urinary stones are primarily the result of bacterial action.

Dr. Moody raised the possibility that we may have unwittingly been studying patients who had Oriental cholangiohepatitis, while intending to focus on stone formation in Western cultures. Only 14 of our patients were of Asian ancestry, and 15 of the white patients lived in England. All of the pigment stones from the English patients showed evidence of bacteria within them. Therefore, we are confident that our conclusions pertain to pigment stone formation in the West.

Lastly, it was asked if this is an infectious process, can it be treated or prevented? There are theoretical possibilities, but nothing that we can think of which would be applicable at the moment. One practical point, however, is that drainage procedures (*e.g.*, choledochoduodenostomy) might be used more liberally in patients with pigment stones.



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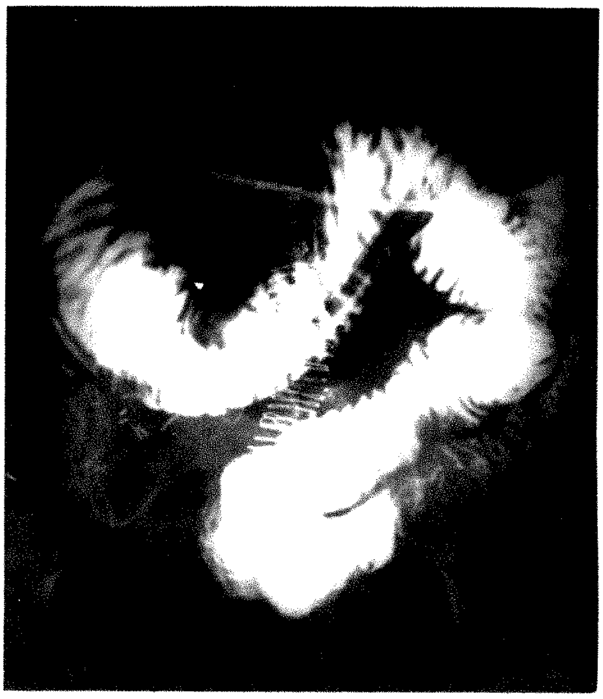
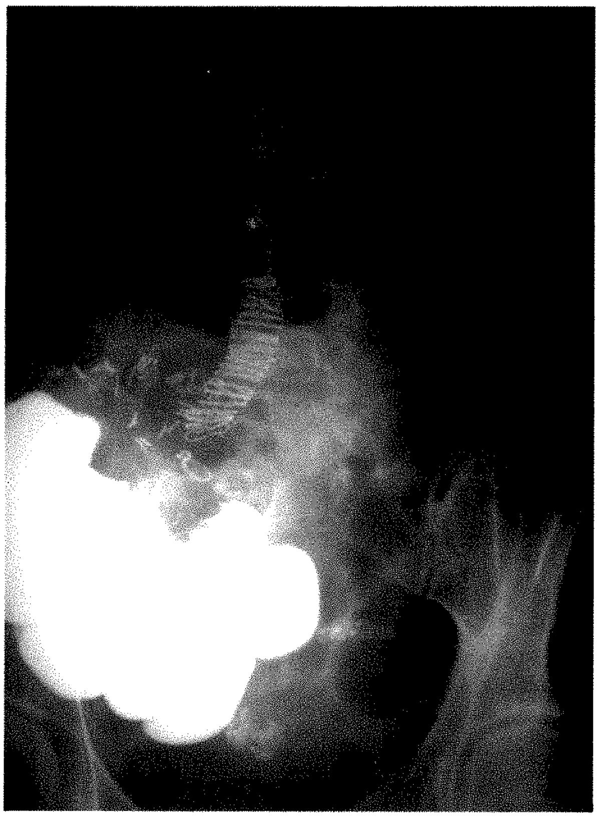
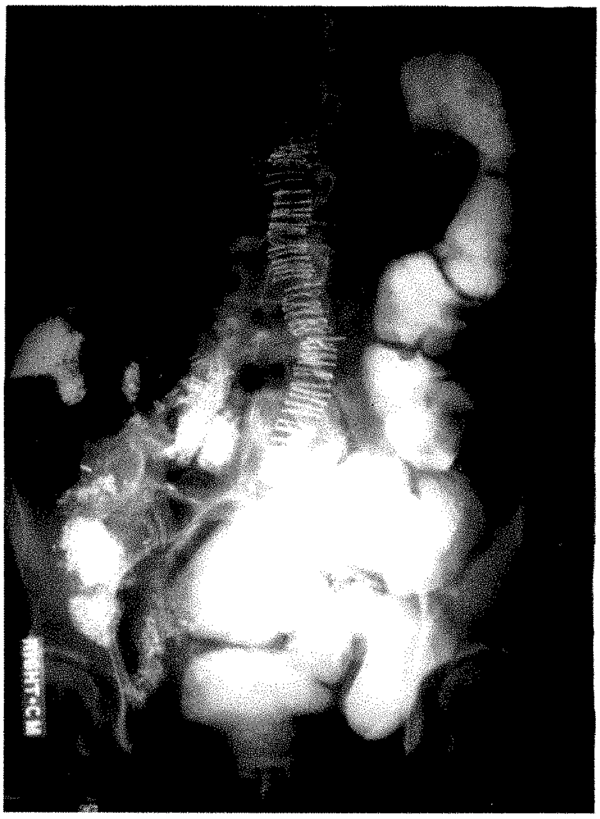
She received 300 ml/hr of Vivonex TEN (Norwich Eaton Pharm), absorbed 5,000 kcal the initial 20 hours, and then tolerated a general diet. She was the 4th patient discharged uneventfully 24 hours after bowel resection and reanastomosis.



A. Study @ 5 minutes (5 hours postop).
Note efficient removal of all excess barium, with none reaching the stomach.



B. Motility @ 4 hours (9 hours postop).
All barium is within the ileum.



C. Motility @ 16 hours (21 hours postop).
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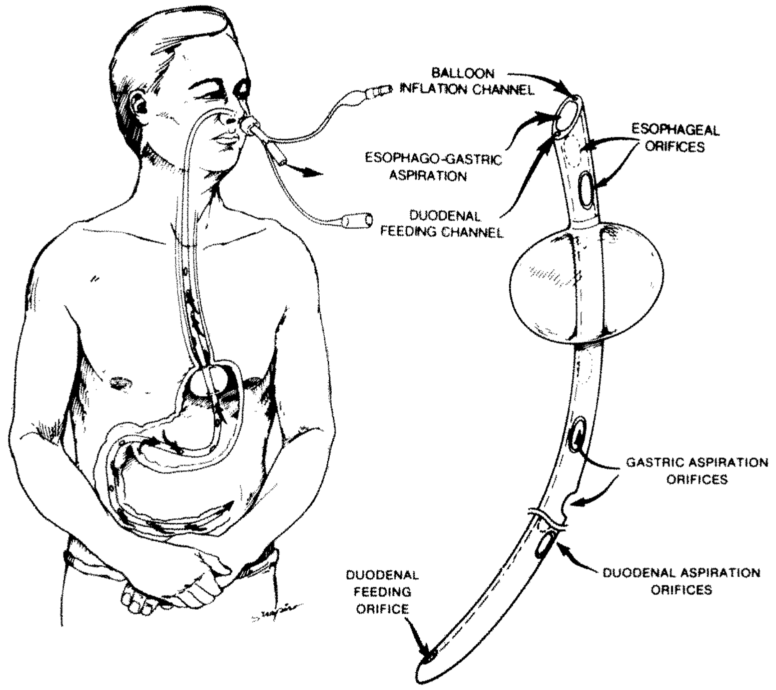
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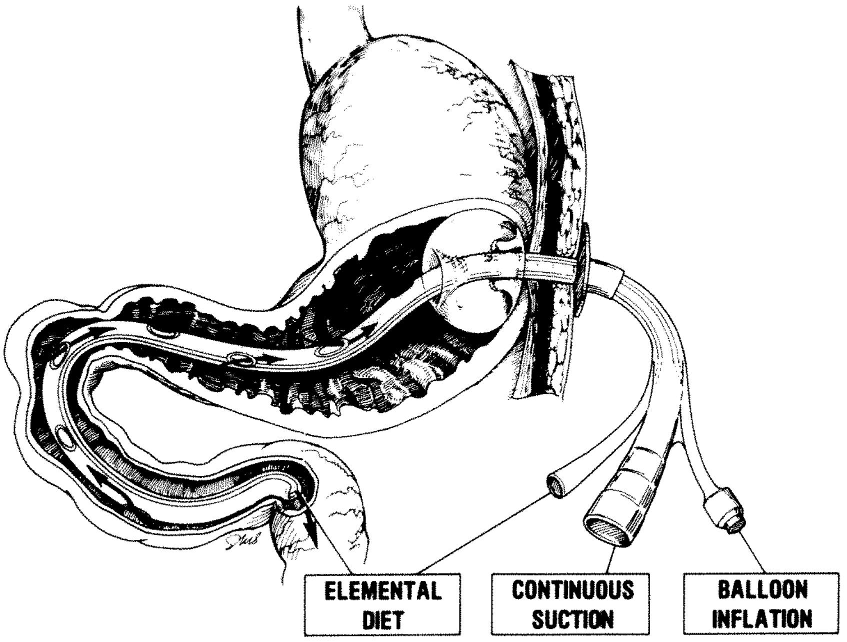

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See brief summary of prescribing information on adjacent page.

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See complete prescribing information in SK&F literature or *PDR*. The following is a brief summary.

Indications: For control of severe nausea and vomiting.

Contraindications: Comatose or greatly depressed states due to C.N.S. depressants; pediatric surgery; use in children under 2 years of age or under 20 lbs.; use in children for conditions for which dosage has not been established.

Warnings: The extrapyramidal symptoms which can occur secondary to 'Compazine' may be confused with the central nervous system signs of an undiagnosed primary disease responsible for the vomiting, e.g., Reye's syndrome or other encephalopathy. The use of 'Compazine' and other potential hepatotoxins should be avoided in children and adolescents whose signs and symptoms suggest Reye's syndrome.

May cause tardive dyskinesia in some patients on neuroleptic (antipsychotic) therapy, usually long-term. This syndrome consists of potentially irreversible, involuntary dyskinetic movements. The risk of tardive dyskinesia and likelihood of irreversibility are thought related to duration of treatment and total cumulative dose of neuroleptic drugs.

Use in patients with bone marrow depression only when potential benefits outweigh risks. Patients who develop a hypersensitivity reaction (e.g., blood dyscrasias or jaundice) to a phenothiazine generally should not be reexposed to any phenothiazine. Caution patients about activities requiring alertness (e.g., operating vehicles or machinery), especially during the first few days' therapy. Prochlorperazine may intensify or prolong the action of other C.N.S. depressants.

Use in pregnancy is not recommended except in cases so serious and intractable that, in the physician's judgment, drug intervention is required and potential benefits outweigh possible hazards. There have been instances of prolonged jaundice, extrapyramidal signs, hyperreflexia or hyporeflexia in newborn infants whose mothers received phenothiazines. There is evidence that phenothiazines are excreted in the breast milk of nursing mothers.

Precautions: The antiemetic action of 'Compazine' may mask the signs and symptoms of overdosage of other drugs and may obscure the diagnosis and treatment of other conditions such as intestinal obstruction, brain tumor and Reye's syndrome (See Warnings). Postoperative aspiration of vomitus has occurred in a few surgical patients who received prochlorperazine as an antiemetic. When used concomitantly with cancer chemotherapeutic drugs, may obscure vomiting as a sign of these agents' toxicity. Deep sleep and coma have been reported with prochlorperazine, usually with overdosage.

Neuroleptic drugs cause elevated prolactin levels that persist during chronic administration. Since approximately one-third of human breast cancers are prolactin-dependent *in vitro*, this elevation is of potential importance if neuroleptic drug administration is contemplated in a patient with a previously detected breast cancer. Neither clinical nor epidemiologic studies to date, however, have shown an association between the chronic administration of neuroleptic drugs and mammary tumorigenesis.

Permanently stop neuroleptic therapy if neuromuscular reactions occur in pregnant women or in children.

In children with acute illnesses or dehydration, use only under close supervision. Avoid high doses and parenteral administration when cardiovascular system is impaired since hypotension has occurred. Use cautiously in patients with glaucoma. Use with caution in persons who will be exposed to extreme heat since phenothiazines may interfere with thermoregulatory mechanisms. Phenothiazines can diminish the effect of oral anticoagulants. Phenothiazines can produce alpha-adrenergic blockade. Thiazide diuretics may accentuate orthostatic hypotension that may occur with phenothiazines. Antihypertensive effects of guanethidine and related compounds may be counteracted when phenothiazines are used concomitantly. Concomitant administration of phenothiazines with propranolol results in increased plasma levels of both drugs and may also precipitate phenytoin toxicity. Phenothiazines may lower the convulsive threshold; dosage adjustments of anticonvulsants may be necessary. Presence of phenothiazines may produce false positive phenylketonuria (PKU) test results. Patients should not receive 'Compazine' 48 hours before or 24 hours after myelography with the contrast medium metrizamide.

Adverse Reactions: Drowsiness, dizziness, amenorrhea, blurred vision, skin reactions. Hypotension. Cholestatic jaundice, leukopenia, agranulocytosis. Fatty changes in the liver have been observed in a few patients who died while receiving the drug (no causal relationship has been established). Neuromuscular (extrapyramidal) reactions: motor restlessness, dystonias, pseudo-parkinsonism, tardive dyskinesia, and a variant, tardive dystonia. Contact dermatitis is a possibility if 'Compazine' Injection (solution) inadvertently gets on hands or clothing.

Other adverse reactions reported with 'Compazine' or other phenothiazines: Some adverse effects are more frequent or intense in specific disorders (e.g., severe hypotension in mitral insufficiency or pheochromocytoma). Grand mal and petit mal convulsions; altered cerebrospinal fluid proteins; cerebral edema; prolongation and intensification of the action of C.N.S. depressants, atropine, heat and organophosphorus insecticides; dryness of mouth, nasal congestion, headache, nausea, constipation, obstipation, adynamic ileus, ejaculatory disorders/impotence, priapism, atonic colon, urinary retention, miosis and mydriasis; reactivation of psychotic processes, catatonic-like states; hypotension (sometimes fatal); cardiac arrest; pancytopenia, thrombocytopenic purpura, eosinophilia, hemolytic anemia, aplastic anemia; biliary stasis; hyperglycemia, hypoglycemia, glycosuria, lactation, galactorrhea, gynecomastia, menstrual irregularities, false positive pregnancy tests; photosensitivity, itching, erythema, urticaria,,eczema up to exfoliative dermatitis; asthma, laryngeal edema; angioneurotic edema, anaphylactoid reactions; peripheral edema; reversed epinephrine effect; hyperpyrexia; mild fever after large I.M. doses; increased appetite; increased weight; a systemic lupus erythematosus-like syndrome; pigmentary retinopathy; neuroleptic malignant syndrome, which may be fatal; with prolonged administration of substantial doses, skin pigmentation, epithelial keratopathy, and lenticular and corneal deposits.

EKG changes have been reported. Discontinue long-term, high-dose therapy gradually.

Note: Sudden death in patients taking phenothiazines (apparently due to cardiac arrest or asphyxia due to failure of cough reflex) has been reported.

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Results with the Mustard Operation in Simple Transposition of the Great Arteries

1963–1985

GEORGE A. TRUSLER, M.D., WILLIAM G. WILLIAMS, M.D., KIM F. DUNCAN, M.D., PETER S. HESSLEIN, M.D., LEE N. BENSON, M.D., ROBERT M. FREEDOM, M.D., TERUO IZUKAWA, M.D., and PETER M. OLLEY, M.D.

From May 1963 to December 1985, 329 infants and children underwent repair of simple transposition of the great arteries (TGA) using Mustard's technique. To assess improvement, the patients were separated into two groups by date of operation: Group I, May 1963 to December 1973 (N = 106), and Group II, January 1974 to December 1985 (N = 223). The operative mortality was 11 (10.4%) in Group I and two (0.9%) in Group II. The 10-year actuarial survival rate was 73.4% in Group I and 93.7% in Group II. Baffle complications, similar in both groups, were identified in 81 patients; 19 were major, causing death or requiring reoperation. By latest electrocardiogram, 21 of 45 (46.7%) of Group I patients and 129 of 180 (71.7%) of Group II patients were in normal sinus rhythm. Late ambulatory electrocardiography, however, revealed that a majority of patients had sinus node dysfunction or other dysrhythmias. Right ventricular (RV) angiography revealed definite diminution of RV contractility in 14 (11%) of 126 children. At late follow-up, 113 of 148 (76%) children were in New York Heart Association (NYHA) Class I and 35 of 148 (24%) were in NYHA Class II. Thirty-five (21%) patients were on cardiac medication chiefly for dysrhythmia management. There has been significant improvement in the early and late mortality with the Mustard operation, and serious baffle complications are infrequent. Dysrhythmias continue to be a major problem but the surviving patients are clinically well and relatively few have significant RV dysfunction.

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MUCH HAS CHANGED in the management of complete transposition of the great arteries (TGA) over the last 25 years. After Mustard[1] first performed his atrial repair in May 1963, there was an immediate awakening of interest in the treatment of TGA. Eventually this lead to a re-examination of other operations, and it was soon found that the Senning[2] atrial repair could produce equally satisfactory results.[3] Later, success was attained with arterial repair, although initially with high mortality.[4] As techniques improved and mortality decreased, arterial repair came to be the preferred treatment in children with TGA and associated ventricular septal defect (VSD).[5,6] Recently arterial repair has been applied to simple TGA in neonates and results are sufficiently competitive to warrant a thorough review of the Mustard procedure.[7–9]

Patients and Methods

From May 1963 to December 1985, at the Hospital for Sick Children in Toronto, 329 infants and children underwent repair of simple TGA using Mustard's technique. This includes children with small inconsequential VSDs or a degree of left ventricular outflow tract obstruction not needing treatment. To assess improvement in results with time, the patients were divided into two groups, those who had repair during the first decade from May 1963 to December 1973 (Group I, N = 106) and those who had repair in the subsequent 12 years from January 1974 to December 1985 (Group II, N = 223) (Table 1).

In the early years, 49% of infants received temporary palliation with a Blalock-Hanlon surgical septectomy. This practice has continued with a higher proportion of atrial septectomies in infants seen initially at our institution than those referred secondarily. The elective age for repair has decreased through the years so that now most Mustard procedures are performed between 6 and 12 months of age.

Originally all repairs were done with cardiopulmonary bypass, but starting in 1972, deep hypothermia and

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TABLE 1. *Mustard Repair of Simple Transposition of the Great Arteries*

	Group I 1963–1973	Group II 1974–1985
Number of patients	106	223
Age at operation	27 days–161 mos	2–131 mos
Mean	37.5 mos	14.25 mos
Previous atrial septectomy	52 (49.1%)	110 (49.3%)
Early deaths	11 (10.4%)	2 (0.9%)
Late deaths	21 (22.1%)	10 (4.5%)

circulatory arrest were used for infants less than 8–10 kg of body weight, which now includes most patients. Since 1976, we have attempted to minimize intraoperative myocardial ischemic damage by giving cold cardioplegia, at first crystalloid and later blood cardioplegia. In addition, the ventricular myocardium has been kept hypothermic with a cold pericardial bath, now replaced by a special cooling jacket.

There have been a few modifications of the original technique. To excise the atrial septum, an incision is first made from the middle of the foramen ovale to the midpoint of the superior vena caval (SVC) orifice. The ridge of tissue medial to the cut is preserved for its potential to allow conduction from the sinoatrial (SA) node to the atrioventricular (AV) node and also to reduce the danger of cutting the artery to the SA node. An earlier study indicated a significant increase in the incidence of sinus rhythm when this ridge of tissue was preserved.[10] All septum lateral (rightward) to the cut is excised. The coronary sinus is cut back and often a small portion of its wall is carefully excised to enlarge the inferior vena caval (IVC) channel. All large raw areas are oversewn to reduce stricture formation and adhesions to the baffle.

Cardiac catheterization was performed after operation in 126 children (Group I, N = 45; Group II, N = 81) with simple TGA to assess baffle problems, as well as tricuspid valve and right ventricular (RV) function.

Cardiac rhythm was assessed primarily by serial electrocardiography, (EKG) but we examined all ambulatory monitor ("Holter") recordings and programmed stimulation electrophysiological studies (EPS) performed on these children. Holter recordings were obtained with a variety of single-channel and dual-channel systems since 1973, with both manual and automated playback systems. Duration of recordings ranged from 6 to 48 hours, but was almost always for a full 24 hours. EPS recordings were all performed since 1981, following standard atrial pacing protocols.[11–13] All studies were obtained with a Honeywell VR 16 recorder (Honeywell, Markham, Canada) and digitalized with an Apple IIe microcomputer using specially designed software (Apple Canada, Toronto, Canada).

TABLE 2. *Early Mortality**

	Group I (N = 106)	Group II (N = 223)
Deaths	11 (10.4%)	2 (0.9%)
Myocardial failure	7	
Dysrhythmia	1	1
Cerebral injury	2	
Bleeding	1	
Air embolism		1

* $p < 0.001$.

For late results in all patients operated on before January 1981, records were reviewed for the last clinical evaluation. Functional assessment was based on symptoms, medications, and school or work history, as well as New York Heart Association (NYHA) grading for patients other than infants. The source of information included chart reviews for follow-up visits, letters from referring physicians, questionnaires to referring cardiologists, and, in 1984, a telephone interview of 128 patients. RV function was assessed at rest and during supine bicycle exercise by gated equilibrium radionuclide angiography in a small group of patients from our institution who had the Mustard procedure, and has been reported previously.[12] Cardiopulmonary function was also measured during upright graded bicycle exercise in a small asymptomatic cohort (N = 17) over 10 years since repair. Actuarial survival curves were calculated using the life table analysis method.

Results

Ten patients in Group I were lost to follow-up (6 after discharge from hospital and one each at 2, 3, 4, and 6 years after operation). Six patients in Group II were lost to follow-up, all at hospital discharge. These patients were included up to the last follow-up date and then excluded but not considered dead statistically.

Early Deaths

Overall mortality (*i.e.,* less than 30 days after operation or before hospital discharge) was 13 of 329 children (4.0%). In Group I, early mortality was 11 (10.4%) of 106 children and in Group II was two (0.9%) of 223 children (Table 2). There have been no early deaths in the 160 patients who had repair since January 1978. In order of frequency, the causes of death were myocardial failure (7), dysrhythmia (2), cerebral injury (2), bleeding (1), and air embolism (1).

Late Deaths

To date there have been 31 late deaths (9.8%) in the 316 operative survivors. In Group I there were 21 (22.1%) late deaths among the 95 early survivors and in Group II there were 10 (4.5%) late deaths in the 221 early survivors (Table 3). Causes of late death include dysrhythmia (9), sudden death (4), pulmonary venous obstruction (8), cardiac failure (5), and other unusual causes that include baffle detachment (1), pulmonary vascular disease (1), pulmonary vein thrombosis (1), congenital respiratory problems (1), and progressive aortic incompetence (1). Three of four children who died suddenly had shown previous rhythm disturbances: two tachyarrhythmias and one intermittent sinus and junctional rhythm. The fourth child was in sinus rhythm shortly after leaving the hospital and no further record was available. Although most late deaths (*i.e.*, 25) occurred within 4 years of operation, there has been a slow attrition with time, late deaths occurring in postoperative years 6, 10, 11, 12, 15, and 18, respectively (all in Group I). These six deaths were due to dysrhythmia (3), sudden death (1), cardiac failure (1), and pulmonary venous obstruction (1).

Actuarial analysis of the 329 children (Fig. 1) shows an 85.8% 10-year survival rate and an 81.5% 15-year survival rate. When the two groups are compared (Fig. 2), Group II patients have a 5- and 10-year survival rate of 93.7% and 93.7%, respectively, compared with the respective rates of 75.4% and 73.4% in Group I patients. Most of the difference is the greatly reduced operative mortality rate from 10.4% to 0.9% ($p < 0.001$), but there is also a difference in the late mortality rate from 22.1% to 4.5% between 1 month and 4 years ($p = 0.025$).

TABLE 3. *Late Mortality**

	Group I (N = 95)	Group II (N = 221)
Deaths	21 (22.1%)	10 (4.5%)
Dysrhythmia	8	1
Sudden death	2	2
Pulmonary venous obstruction	5	3
Cardiac failure	3	2
Other	3	2

* $p = 0.025$.

Postoperative Cardiac Catheterization Data

Baffle Complications

Baffle leaks, although relatively common, are usually small and inconsequential, remaining unidentified until discovered by cardiac catheterization or echocardiography. There were 316 early survivors after Mustard repair of simple TGA; 126 (45 in Group I, 81 in Group II) had at least one postoperative cardiac catheterization (Table 4). In 40 survivors (12.7% but 31.7% of those catheterized), a baffle shunt was found (22 in Group I, 18 in Group II). Most were small but in five survivors the shunt was large. One child died and two children required reoperation.

Of the 316 early survivors, 26 (8.2%) were found to have some narrowing of the SVC channel. Seven were Group I patients and 19 were Group II patients. In 15 of the 26 children, this was mild; it is likely that more follow-up catheterization studies would uncover mild SVC stenosis in other asymptomatic patients. More severe degrees of stenosis were encountered in 11 patients, four with gradients of 5–8 mmHg across the stenosis and six with gradients over 8 mmHg. One child had complete obstruction but was asymptomatic due to run-off

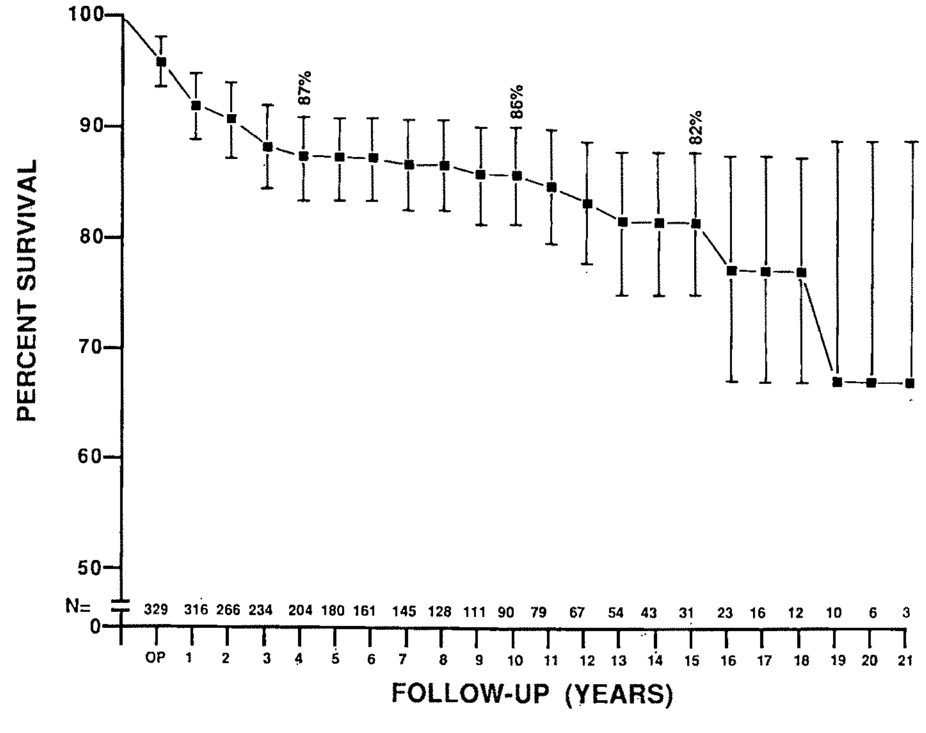

FIG. 1. Actuarial analysis of survival after the Mustard operation in simple TGA for 329 children between 1963 and 1985. The survival rate is 85.8% at 10 years and 81.5% at 15 years.

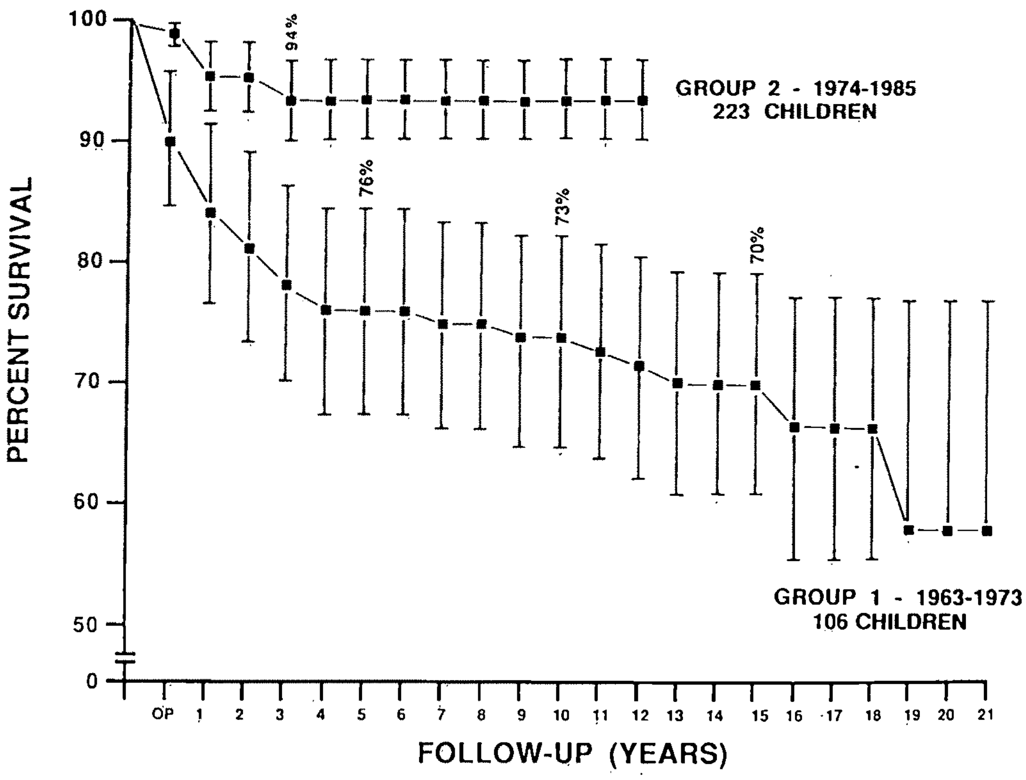

FIG. 2. Graph comparing survival in Group I and Group II patients. Group II patients had a 5- and 10-year survival rate of 93.7% compared with 75.4% and 73.4% in Group I patients.

through the azygos vein. Only two children required revision of the baffle to relieve SVC stenosis.

IVC stenosis was identified in three (0.9%) of the 316 early survivors: two in Group I and one in Group II. One child had mild IVC stenosis but two required repair.

Partial obstruction of pulmonary venous channels was encountered in 12 (3.8%) of the 316 early survivors. In six children (4 in Group I, 2 in Group II), all of whom died, stenosis occurred at the plane of the original atrial septum, the baffle apparently adhering to the area of septal excision and then contracting to obstruct venous return from all four veins. In the other six children (2 in Group I, 4 in Group II), the stenosis was more posterior in the left atrium, between the entrance of the right and left pulmonary veins, obstructing only the left pulmonary veins. Five of these children survived repair but one died later. Ostial stenosis of the pulmonary veins was found at reoperation in six children with pulmonary venous obstruction, and was not only difficult to repair but persisted in all. Ostial stenosis of the left pulmonary veins, with no apparent preceding cause, was found at the time of the Mustard operation in two other children.

In total, there were 81 baffle "problems" identified among the 316 early survivors of the Mustard operation. Although most were minor in nature, 14 (4.4%) children required reoperation and there were nine deaths: four after reoperation and five without reoperation.

Other Complications

At late cardiac catheterization (126 cardiac catheterization studies) other problems were noted. Left ventricular outflow tract stenosis with a left ventricular–pulmo-

TABLE 4. *Baffle Complications*

	Group I	Group II	Total	% of Survivors	% of Catheters
Early survivors	95	221	316		
Number of catheterized	45	81	126	39.9	
Baffle leaks	22	18	40	12.7	31.7
SVC stenosis	7	19	26	8.2	20.6
IVC stenosis	2	1	3	0.9	
Pulmonary vein stenosis	4	2	6	1.9	
Isolated LPV stenosis	2	4	6	1.9	

nary artery (LV–PA) gradient over 10 mmHg was found in 24 children. This was mild in 19 children with a gradient less than 26 mmHg. The other five children had a gradient ranging from 26 to 58 mmHg. Thirteen children were found to have pulmonary hypertension. In five children this was related to obvious problems; pulmonary venous obstruction (2), pulmonary vein thrombosis (1), recurrent chest problems (1), and pulmonary vein stenosis (1), and all five children subsequently died. Seventeen children had a small VSD that had been ignored intentionally at the time of Mustard repair.

Postoperative Rhythm Status

Late electrocardiographic follow-up at least 1 year after operation was available in 225 children of whom 150 (66.7%) were in sinus rhythm (Table 5). Of 41 Group I patients, 21 (46.7%) were in sinus rhythm. In Group II, 92% were in sinus rhythm at the time of discharge from the hospital and 129 (71.7%) of 180 children were in sinus rhythm by last electrocardiogram. Pacemakers were inserted in seven children, four in Group I and three in Group II. In five children the pacemakers were required for sick sinus syndrome and in two children pacemakers were required for SA/AV node dysfunction.

The discharge electrocardiograms of 39 patients who had Blallock-Hanlon septectomy between 1981 and 1984 were reviewed. Although 35 patients were in normal sinus rhythm, four showed abnormalities of rhythm, junctional rhythm, sick sinus syndrome, first degree A-V block, and low atrial pacemaker, respectively. Electrocardiograms just before Mustard repair revealed a similar incidence of rhythm problems predating repair.

A total of 216 Holter recordings were obtained after Mustard repair in 126 patients (Table 6). These included 23 Group I patients (35 recordings) and 103 Group II patients (181 recordings). The mean interval between operation and Holter recording was 148.4 months for Group I and 27.3 months for Group II. Although sinus rhythm was witnessed in 114 patients (90.5%), it was by no means the predominant rhythm exhibited in this series. The predominant cardiac rhythm was a junctional bradycardia or atrial flutter in 60% of Group I patients and 52% of Group II patients. Among the 40% of Group I children in a predominantly atrial rhythm (including sinus), three had a wandering atrial pacemaker and four had bursts of supraventricular tachycardia (SVT). Similarly, among the 48% of Group II children with a predominant atrial rhythm, 19 had a wandering atrial pacemaker and seven had SVT. A variety of ventricular arrhythmias were seen in both groups of patients, including ventricular tachycardia.

TABLE 5. *Postoperative Rhythm: Last EKG*

	Group I (1963–1973)	Group II (1974–1985)	Total
Sinus rhythm	21 (46.7%)	129 (71.7%)	150 (66.7%)
Junctional rhythm	6 (13.3%)	33 (18.3%)	39 (17.3%)
Sick sinus syndrome*	10 (22.2%)	6 (3.3%)	15 (6.7%)
Wandering pacemaker		7 (3.9%)	7 (3.1%)
Atrial flutter	6 (13.3%)	3 (1.7%)	9 (4.0%)
SA/AV node dysfunction*	2 (4.4%)	2 (1.1%)	5 (2.2%)
Total	45	180	225

* Includes seven patients with pacemakers.

Twenty-two children had multicatheter EPS an average of 52.5 months after operation (Table 7). There were four patients from Group I and 18 from Group II; four studies were indicated to investigate symptomatic rhythm disturbances, whereas the other 18 were considered "routine" postoperative investigations. It is clear that sinus node function was frequently suppressed in this group of patients and some demonstrated subtle abnormalities of A-V node function.

To determine whether the EKG and EPS changes after the Mustard operation were progressive or detectable at the time of the procedure, 23 children were studied prospectively with preoperative baseline catheter EPS, followed by EPS on postoperative days 1, 3, and 8, performed at the bedside using routinely placed epicardial temporary pacing wires (Table 8). The only EPS abnormalities before operation pertained to the sinus node and atrial muscle function of children with a prior Blalock-Hanlon septectomy. By contrast, abnormal studies were frequent after the Mustard operation, with the majority of these changes persisting to day 8.

TABLE 6. *Cardiac Rhythm after Mustard Operation: Ambulatory Recordings*

	Percentage of Patients	
	Group I (N = 23)	Group II (N = 103)
Supraventricular rhythms		
Sinus rhythm present	83	92
Predominant sinus rhythm	37	29
Wandering atrial pacemaker	3	19
Predominant junctional rhythm	43	45
Predominant atrial flutter	17	7
Premature supraventricular extrasystoles	43	49
Supraventricular tachycardia present	4	7
Other rhythms noted		
2° atrioventricular block	13	4
3° atrioventricular block	0	1
Premature ventricular contraction noted	65	57
Ventricular couplets noted	17	9
Ventricular tachycardia	9	3

TABLE 7. *Cardiac Rhythm after Mustard Operation: Late Postoperative EPS Findings*

	Percentage of Patients	
	Group I (N = 4)	Group II (N = 18)
Sinus node function		
Good	0	17
Fair	25	44
Poor	75	39
A-V node function		
Good	25	50
Fair	50	44
Poor	25	6
Atrial flutter (present or inducible)	75	22

RV Function

A subjective estimation of RV contractility was made by the radiologist and/or the cardiologist from the RV angiograms of 126 children with isolated TGA (Table 9). Forty-two children appeared to show some alteration in RV contractility but in only 14 of 126 (11%) children was this considered definite and rated as moderate (10) or severe (4) diminution in RV contractility. Subsequently two children died of cardiac failure. Thirteen (10.3%) of the 126 children had mild tricuspid incompetence, four with and nine without obvious RV dysfunction. Eight of the children with RV dysfunction were in Group I and six were in Group II. The difference in incidence is not significant by actuarial analysis (p = 0.076).

Fourteen Group I patients underwent supine radionuclide bicycle exercise with estimation of RV ejection fraction.[14] At rest, the RV ejection fraction averaged 46 ± 11% with no significant change at peak exercise, 48 ± 12%. Additionally, there was an inappropriate response of blood pressure, rising only 18 ± 15% of resting values. The cardiopulmonary response to exercise was studied in 17 asymptomatic Group I patients during upright bicycle exercise. During incremental increase in work, the TGA patients, as compared with age-matched controls, had lower work capacities, heart rates, and oxygen consumptions, but minute ventilation was normal. Cardiac output was within the normal range at 50% maximal stress, thus suggesting reduced aerobic capacity for exercise.

TABLE 8. *Cardiac Rhythm after Mustard Operation: Acute Perioperative EPS Changes*

	Percentage of Patients (N = 23)		
	Preoperative	Transient Postoperative	Persistent Postoperative
Sinus node dysfunction	13*	22	52
A-V node dysfunction	0	4	17
Inducible SVT/flutter	9*	0	22†

* All patients in these categories had undergone a prior Blalock-Hanlon atrial septectomy.

† To date, 60% of these subjects with inducible arrhythmias have experienced subsequent spontaneous clinical arrhythmias of a similar nature; no clinical arrhythmias have so far occurred among "uninducible" patients.

TABLE 9. *Right Ventricular Problems*

	Group I (45 Studies)	Group II (81 Studies)
RV dysfunction, moderate to severe	6	4
RV dysfunction plus TV incompetence	2	2
TV incompetence alone	4	5

Clinical Status

Of 148 patients for whom adequate information on clinical status was available, 113 (76%) were in NYHA Class I and 35 (24%) were in Class II (Table 10). None were in Class III or IV. Information regarding medication was obtained in 167 patients. Seventy-nine per cent were not receiving any medication. Thirty-one patients were receiving digitalis for dysrhythmia management. One patient was receiving digitalis and diuretic for fluid retention. Two children were taking inderol for dysrhythmia and one patient was receiving nitroglycerin for intermittent chest pain associated with dysrhythmia. No surviving patients were in uncontrolled congestive heart failure.

Information regarding school and work experience indicated a performance similar to that found in children after other cardiac operations. Most of the 169 patients reviewed were at school or employed. One hundred fifteen children were in an appropriate school grade, eight attended college, and five were considered exceptional students. Thirty-seven children had repeated at least one grade at school and seven patients required special education classes. There were 15 patients with neurologic abnormalities after surgery: hemiparesis (7), mental retardation with seizure disorder (4), cerebral palsy (1), and other seizure disorders (3). In 10 of the 15 children, the neurologic abnormality

TABLE 10. *Clinical Status*

	Group I	Group II	Total
NYHA Class I	37	76	113 (76%)
NYHA Class II	21	14	35 (24%)
NYHA Class III or IV	0	0	0
On cardiac medication	18	17	35 (21%)
No cardiac medication	28	104	132 (79%)

preceded the transposition repair, but in the other five children the problem seemed related to the operation, although in two cases it was not noted for several months.

Discussion

There has been a notable decline in the early mortality with the Mustard operation in isolated TGA until it is now virtually zero with no deaths in the last 160 patients operated on since January 1978. Other authors have also reported very low mortality.[15-20] Late mortality has also decreased with 10 deaths in the 221 early survivors since January 1974, giving a 10-year survival rate of 93.7%. Statistical comparison with our earlier experience indicates that this is significant ($p = 0.025$). The reason for the improvement can only be surmised to include more efficient and effective operation, improved myocardial protection, and improved postoperative management of dysrhythmias and other complications.

Baffle complications have been reported frequently[15,17,20-25] and they continue to occur, although perhaps at a slightly lower rate. Certainly it is our impression that baffle leaks are less frequent, although still the most common of the baffle complications. Serious degrees of SVC obstruction are less frequent but mild SVC stenosis has been seen more often since 1974, when we began leaving a ridge of atrial septum between the SVC and the tricuspid valve to reduce rhythm disorders. Similarly, stenosis of the IVC channel is seldom seen and there have been no new instances of this complication for many years. To prevent caval stenosis we use a pericardial baffle that is moderately redundant at both caval orifices, and suture carefully to avoid leaks that might allow contraction of the baffle and narrowing of the caval channel.

Narrowing of the pulmonary venous channel is a serious complication.[23-25] In recent years obstruction affecting both right and left veins at the level of the original atrial septum has been less frequent than earlier years. Obstruction of the left pulmonary veins occurred in six children and appears to result from placing the upper and lower baffle suture lines too close to each other, on the posterior wall of the left atrium, a maneuver intended to enlarge the caval channels. Of 316 early survivors of the Mustard operation for simple TGA, 19 (6.0%) children had baffle complications that required reoperation or caused death. Possibly impeccable operative techniques would reduce this problem further, but some risk of these complications appears inherent to the procedure. In general, a moderately redundant baffle seems to work well, and the most important detail seems to be the position and integrity of the baffle suture line.

Dysrhythmias, the most frequent problem after the Mustard operation, accounted for late death in nine patients and are assumed to be the cause in four other patients who died suddenly. Ten (10/95) of these 13 deaths were in Group I patients and the other three (3/221) were in Group II patients. The primary problem is sinus node dysfunction, and atrioventricular conduction is usually intact.[13] Our overall results from analysis of the last electrocardiogram at least 1 year after operation revealed that 66.7% of children were in sinus rhythm, whereas the remainder demonstrated evidence of sinus node dysfunction, junctional rhythm, or in a few cases more serious problems such as atrial flutter or AV node dysfunction. In our earlier report we noted that a change in technique, which preserved a ridge of atrial septum between the SVC and TV, increased the incidence of sinus rhythm.[10] Indeed, the incidence of sinus rhythm was greater in Group II patients than in the earlier group. Several authors[26,27] suggest, however, that the incidence of dysrhythmia increases with time; therefore, perhaps the improvement will not last. Stark et al. found 59% with normal sinus rhythm on 24-hour monitoring 2 weeks after repair.[28] Bierman et al.[29] in a series that included complex TGA reported only 30% of patients free of arrhythmias 9 years after repair, but symptoms from rhythm or conduction disturbances were rare. In our experience only about one quarter of children with abnormal rhythms are symptomatic. Also, this information should be kept in perspective for even after simple ASD repair normal sinus rhythm was found in only 78% of patients.[30]

The data derived from the Holter and EPS studies is also less optimistic for it appears that stable sinus rhythm is less frequent than previously believed. Despite the technical changes in operative technique designed to preserve the sinus node, there is no appreciable difference in the prevalence of arrhythmias on Holter recordings from patients repaired before and after these modifications. Moreover, the comparable occurrence rates of arrhythmias on Holter tapes for Groups I and II, despite the large difference in mean postoperative intervals (148.3 months *vs.* 27.3 months, respectively) suggest that the appearance of rhythm disturbances may not be as progressive as suggested by others.[26,27] This notion is supported by the results of our prospective study in 23 children with perioperative EPS. These children will be the subject of ongoing surveillance, but it is interesting that the prevalence of their early postoperative EPS abnormalities is so similar to that of the other group studied an average of 52.5 months after surgery to suggest that the conduction system abnormalities caused by the Mustard operation are detectable early after surgery, even if the clinical manifestations appear later. The ongoing problems with persistent or recurring atrial flutter, pacemaker dependency, and other dysrhythmias confirm that cardiac rhythm disorders represent a major shortcoming of the Mustard operation.

Postoperative RV function has also been a concern to everyone dealing with TGA patients. Early death and myocardial failure are infrequent now and most children do not require inotropic support after operation. However, the details of management, particularly duration of myocardial ischemia, are important. It is our impression that when repair is done on infants less than 3 months old, there is an increased incidence of myocardial failure and need for inotropic support. By comparison, an infant or child having an arterial switch repair seems to accept a relatively long period of myocardial ischemia. It seems that the right ventricle cannot tolerate the same duration of myocardial ischemia as the left ventricle and still support systemic pressures. Cardiac failure was the cause of late death in five of 31 children with simple TGA and the most common cause of late death in complex TGA. It likely results from the cumulative effect of all the damaging events that influence the right ventricle before, during, and after the repair. This may include not only the obvious effect of any myocardial ischemic interval but also the insidious effects of various events associated with less than optimum myocardial perfusion, such as a low output state after operation or an abnormal cardiac rhythm with bradycardia or tachycardia. Furthermore, that most late deaths occurred within 4 years of repair suggests a relationship to the operation. There was only one late death of cardiac failure more than 4 years after operation.

We have attempted to detect abnormalities of RV contractility from the angiographic appearance at cardiac catheterization, but unfortunately this subjective grading does not provide an accurate measurement. Although some alteration in RV contractility was suspected in almost one third of the 126 children who had late cardiac catheterization with angiocardiography, only 14 (11%) showed definite RV dysfunction. Two children died subsequently but the others have remained asymptomatic. More objective evaluation in a small cohort of Group I patients suggested impairment in the ability of the RV to function appropriately under the stress of exercise as compared with normals.[14]

There have been many studies of RV function after atrial repair of TGA and the ultimate significance is still not clear. Abnormal size and ejection fraction of the RV after atrial repair was noted.[31-33] Using gated equilibrium nuclear angiography, Benson et al.[14] evaluated the RV function response to the stress of supine bicycle exercise an average of 6.4 years after the Mustard operation. Although clinically well, 11 of 19 children had an abnormal response with a decrease or at least no increase in RV ejection fraction. Similar results were obtained by others.[34-36] Parrish et al.[37] also noted an abnormal left ventricle (LV) repsonse to exercise in 10 of 11 children tested after a Mustard repair and concluded that biventricular dysfunction was frequently present. In each study some children had normal RV function at rest and during exercise, which suggests that the RV problem may not be inevitable. Indeed, Benson et al.[38] recently reported normal systemic ventricular function in patients with congenitally corrected TGA. Ramsay et al.[39] found an abnormal response to exercise by both RV and LV after Mustard repair but found no predictable correlation with clinical or hemodynamic criteria. Graham and co-workers,[40] comparing groups of patients after atrial repair of simple TGA, found an improvement in the postoperative RV ejection fraction in patients operated on after 1974, whether by Mustard or Senning technique compared with patients operated on previously. They suggest that this improvement may be due to a younger age at surgery and/or changes in operative technique, particularly myocardial protection. Smith et al.,[41] however, caution that the general architecture of the ventricular mass and the atrioventricular valves is different from normal and the function of the normal heart may not always be an appropriate yardstick for comparison.

Tricuspid valve incompetence was not a major problem. It was found in only 13 (10%) children who had cardiac catheterization after operation, four in association with RV dysfunction. Tricuspid valve incompetence is more common in children who have had repair of an associated VSD,[24] undoubtedly due to distortion of the valve by the repair in some cases. Occasionally the tricuspid incompetence is present before repair.[36] Deal et al.[42] found tricuspid valve abnormalities were frequent in patients with TGA and VSD but were rare in isolated TGA. Tynan et al.[43] reported postoperative tricuspid incompetence secondary to arrhythmia in some patients. Thus, the tricuspid incompetence in children after simple TGA repair appears to be related to either RV dysfunction, arrhythmia, or in rare cases pre-existing tricuspid valve abnormalities.

The general clinical status of most patients is good. Almost all patients exhibit normal growth after repair.[20,21] In our series 76% were in NYHA Class I and 24% in NYHA Class II. Although 79% were not taking cardiac medications, 21% were, nearly all for dysrhythmia management. Although it is our impression that these children are not generally athletic, most are unrestricted and some take part in athletic events. Stark et al.[28] found that exercise performance of asymptomatic patients who appeared to be living normal lives 6–13 years after Mustard's operation was somewhat diminished compared with a group of normal children, as our cardiopulmonary exercise testing has also shown. There was no significant difference between the group of patients who had their Mustard operation in infancy and later. Mathews et al.[44] conducted exercise studies in children after Mustard repair and found that, although no patients had subjective exercise intolerance before the test, the exercise tolerance was decreased in half, with maximum oxygen consumption values lower than controls.

This paper is not intended to compare in detail our results with the Mustard procedure with those of others. Indeed it would be difficult to do so effectively for we have focused on children with simple transposition, to present a clearer picture since the incidence of dysrhythmia, tricuspid incompetence, and RV dysfunction is higher after repair of TGA with VSD. Similarly we have deliberately avoided comparing the Mustard and Senning operations. Many authors have reported excellent results with the Senning procedure[45–47] but there are few long-term series for comparison. We believe that there is little difference in the results of the two procedures and that most of the complications and problems encountered after the Mustard procedure will also occur with the Senning operation.

Our main purpose in this presentation has been to describe the early and late results of the Mustard procedure and indicate both the current status and the improvements that have occurred. With this information the comparison with arterial switch repair can be made on a more rational basis. Arterial repair in the newborn, a technically demanding procedure, has been performed with low risk by some surgeons.[7–9,48] Interim problems and the need for repeat operations are as common if not more common than after the Mustard operation in our experience. The main appeal of arterial repair is the expected low incidence of major late complications such as dysrhythmias, tricuspid incompetence, and RV dysfunction, which may lead to late morbidity and death. The chief concern is whether the early results of a few surgeons can be reproduced by others without excessive risk. We hope this paper presents a fair summary of what atrial repair can offer the infant with simple TGA.

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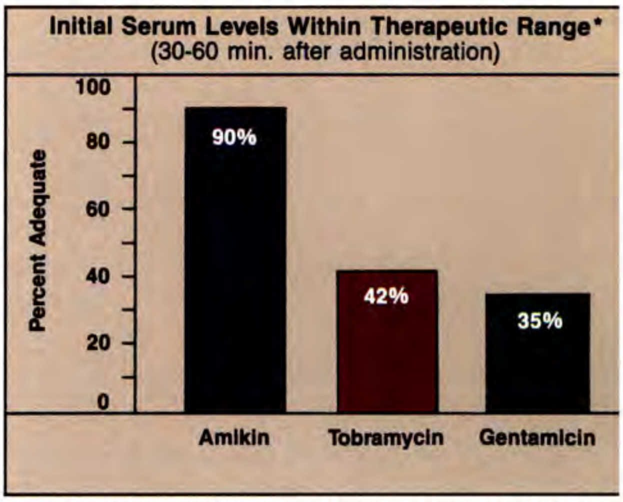

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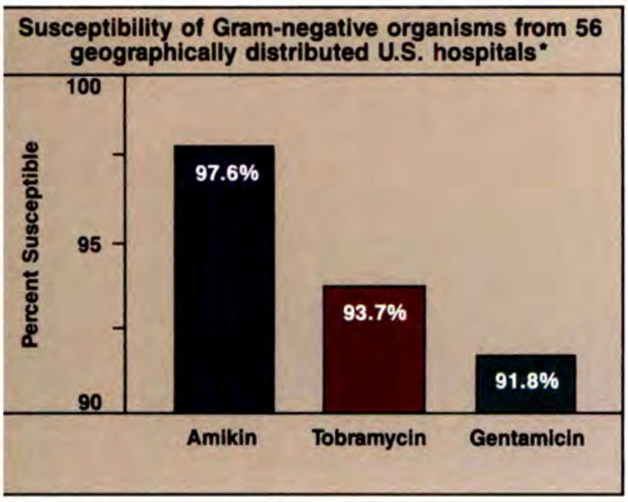

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AMIKIN is potentially nephrotoxic, ototoxic, and neurotoxic. The concurrent or serial use of other ototoxic or nephrotoxic agents should be avoided either systemically or topically because of the potential for additive effects. Such agents include antibacterial drugs such as kanamycin, gentamicin, tobramycin, neomycin, streptomycin, cephaloridine, paromomycin, viomycin, polymyxin B, colistin and vancomycin as well as certain diuretic agents such as ethacrynic acid or furosemide.

Ototoxicity — See "Warning" box.

Nephrotoxicity — Since AMIKIN is present in high concentrations in the renal excretory system, patients should be well hydrated to minimize chemical irritation of the renal tubules. Kidney function should be assessed by the usual methods prior to starting therapy and daily during the course of treatment.

If signs of renal irritation appear (casts, white or red cells or albumin), hydration should be increased. A reduction in dosage (see "Dosage and Administration") may be desirable if other evidence of renal dysfunction occurs such as decreased creatinine clearance, decreased urine specific gravity, increased BUN, creatinine or oliguria. If azotemia increases or if a progressive decrease in urinary output occurs, treatment should be stopped.

Note: When patients are well hydrated and kidney function is normal the risk of nephrotoxic reactions with amikacin is low if the dosage recommendations (see "Dosage and Administration") are not exceeded.

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Other — Cross-allergenicity among aminoglycosides has been demonstrated. As with other antibiotics the use of amikacin may result in overgrowth of nonsusceptible organisms. If this occurs, appropriate therapy should be instituted.

Pregnancy — Reproduction studies have been performed in rats and mice and have revealed no evidence of impaired fertility or harm to the fetus due to amikacin. There are no well-controlled studies in pregnant women but investigational experience does not include any positive evidence of adverse effects on the fetus. Although there is no clearly defined risk, such experience cannot exclude the possibility of infrequent or subtle damage to the fetus. AMIKIN should be used in pregnant women only when clearly needed.

It is not known whether this drug is excreted in human milk. As a general rule, nursing should not be undertaken while a patient is on a drug since many drugs are excreted in human milk.

ADVERSE REACTIONS

Ototoxicity — See "Warning" box.

Nephrotoxicity — Albuminuria, presence of red and white cells, casts, azotemia and oliguria have been reported.

Other — In addition to those described above, other adverse reactions which have been reported on rare occasions are skin rash, drug fever, headache, paresthesia, tremor, nausea and vomiting, eosinophilia, arthralgia, anemia, hypotension.

Overdosage — In the event of overdosage or toxic reaction, peritoneal dialysis or hemodialysis will aid in the removal of amikacin from the blood.

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*"Cancer of the Colon and Rectum: Summary of Public Attitude Survey," *Ca* 33:359-365, 1983 (Nov.-Dec.).

Shunt Surgery *Versus* Endoscopic Sclerotherapy for Long-term Treatment of Variceal Bleeding

Early Results of a Randomized Trial

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In September 1982, a prospective randomized trial comparing shunt surgery and endoscopic sclerotherapy for the elective management of variceal hemorrhage in patients with cirrhosis was initiated. Twenty-seven patients have received shunts (distal splenorenal = 23, nonselective = 4) and 30 patients have had chronic sclerotherapy. Eighty-six per cent of patients had alcoholic cirrhosis and 33% were Child's class C. After a mean follow-up of 25 months, 19% of shunt and 57% of sclerotherapy patients have had rebleeding (p = 0.003). Kaplan-Meier survival analysis reveals similar 2-year survival rates for shunt (65%) and sclerotherapy (61%) groups. Only two of 10 sclerotherapy failures have been salvaged by surgery. Posttherapy quantitative hepatic function, frequency of encephalopathy, and cumulative medical costs were similar for both groups. Hepatic portal perfusion and portal pressure at 1 year were better maintained by sclerotherapy than by distal splenorenal shunt. In conclusion, endoscopic sclerotherapy and shunt surgery provide similar results with respect to survival, hepatic function, frequency of encephalopathy, and costs. Sclerotherapy is an acceptable, but not superior, alternative to shunt surgery for treatment of variceal hemorrhage.

THE IDEAL THERAPY for variceal hemorrhage would permanently eliminate this life-threatening complication of portal hypertension and have no adverse effects on hepatic physiology. Unfortunately, no single treatment provides both of these advantages. Surgical portal decompression reliably prevents future bleeding episodes, but alters liver perfusion. Endoscopic sclerotherapy and nonshunting operations minimally influence hemodynamic function, but are generally followed by a higher frequency of recurrent hemorrhage than portal-systemic shunts.

The distal splenorenal shunt (DSRS) is the only commonly used shunting procedure with the capacity of maintaining hepatic portal perfusion. Several controlled trials[1-3] comparing the DSRS to various nonselective shunts have demonstrated a lower frequency of encephalopathy after selective variceal decompression. Based on these studies, as well as other large uncontrolled series,[4,5] the DSRS has emerged as the preferred procedure for most patients when surgical therapy is indicated for variceal hemorrhage. Because some patients, *e.g.*, those with medically intractable ascites, are not candidates for the DSRS, we have evolved a selective operative approach, selecting the type of shunt (DSRS, end-to-side portacaval shunt, or side-to-side portal-systemic shunt) based on each individual's clinical and hemodynamic circumstances.[6]

Because of dissatisfaction with portal decompression and its adverse consequences of encephalopathy and hepatic failure, endoscopic sclerotherapy was reintroduced in the 1970s, first for the emergency management of bleeding varices and subsequently as definitive treatment to prevent recurrent hemorrhage. Several controlled trials[7-10] of sclerotherapy *versus* conventional medical management have shown a beneficial effect of this treatment on frequency of rebleeding, and some trials[7,9] have demonstrated prolonged survival after sclerotherapy.

The current investigation was designed to determine whether shunt surgery (selective approach) or chronic endoscopic sclerotherapy is preferable for patients with cirrhosis who bleed from varices. Only patients who survived their initial hemorrhage are included. Thus,

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elective rather than emergency therapies are compared. Based on previous controlled studies of treatments for variceal hemorrhage in predominantly alcoholic cirrhotic populations, it was anticipated that these two therapies might result in similar survival rates. Therefore, multiple variables were carefully studied to determine the relative impact of these treatment modalities on hepatic functional reserve, hepatic hemodynamic status, psychoneurologic function, and medical costs.

Methods

Patients

The study population comprised 57 patients with cirrhosis and variceal hemorrhage referred between September 1982, and December 1986. During the first 2 years, patients were accrued from the University of Utah Medical Center (N = 18) and Salt Lake Veterans Administration Medical Center (N = 17). After the principal investigator moved to the University of Nebraska Medical Center in August 1984, study patients were derived from that institution (N = 10) and from the Omaha Veterans Administration Medical Center (N = 12). The study population was drawn from a pool of 150 patients who were treated for variceal hemorrhage by surgery or endoscopic sclerotherapy at these four hospitals during these intervals. To be considered for randomization, each patient had to meet the following criteria: (1) historic, clinical, and/or laboratory evidence of cirrhosis (diagnosis confirmed by biopsy in all patients); (2) endoscopic documentation of acute or recent variceal hemorrhage (actively bleeding varix or large nonbleeding varices with no other lesions) requiring at least three units of blood transfusion; (3) residence within 500 miles of Salt Lake City or Omaha; (4) cessation of acute variceal hemorrhage either spontaneously or by use of one or a combination of intravenous vasopressin infusion, balloon tamponade, and emergency endoscopic variceal sclerosis; and (5) patency of the splanchnic venous system demonstrated by visceral angiography. Patients bleeding from gastric varices located more than 2 cm from the esophagogastric junction were excluded. After stabilization from the acute bleeding episode, patients who met the above criteria and who agreed to participation after informed consent were randomized using Efron's biased coin design,[11] based on three liver function strata (modified Child's classification) and type of hospital (University or Veterans Administration). Twenty-eight patients were randomized to shunt surgery and 29 patients were randomized to endoscopic sclerotherapy. One patient refused surgery and was treated with endoscopic variceal sclerosis. In all subsequent analyses, this individual is included in the sclerotherapy group (N = 30; shunt group, N = 27).

Therapy

Selection of shunt was based on each individual's clinical circumstances and hepatic hemodynamic status.[6] Patients with compatible anatomy (splenic vein greater than 7 mm), hepatopetal portal flow on preoperative angiography, and either absent or medically controllable ascites received the DSRS (N = 23). Individuals with ascites intractable to medical management or spontaneous reversal of portal flow on preoperative angiography had a side-to-side portal-systemic shunt (N = 3). Side-to-side shunts used included the side-to-side portacaval shunt (N = 1) and Dacron graft (16–20 mm) interposition shunts (N = 2) in the portacaval or mesorenal positions. A single end-to-side portacaval shunt was done emergently in a patient who massively rebled after randomization. All shunts were constructed by a single surgeon (LFR).

Endoscopic sclerotherapy was performed with a standard upper gastrointestinal flexible endoscope without accessories. During the first 2 years of the investigation, 0.75% sodium tetradecyl sulfate in 50% dextrose was used as sclerosant because 5% sodium morrhuate, which has been used during the last 2 years, was not then available. Intravariceal injections of all columns just above and at 5 cm proximal to the esophagogastric junction were accomplished at the initial session. Approximately 2 mL of sclerosant per injection with a maximum of 20 mL per session was used. Sclerotherapy was repeated at 4- to 6-day intervals until most varices were eradicated. Follow-up endoscopy was scheduled for 4–6 weeks after the last session and then at 6-month intervals unless recurrent hemorrhage intervened. The 30 sclerotherapy patients had 6.7 ± 0.8 SEM sclerosis treatments per patient with a range from 1 to 23 treatments. Eighty per cent of patients were compliant and returned for endoscopy as scheduled. Varices were completely eradicated in 19 patients (63%), but reformed in 12 of these individuals. The only major complication of sclerotherapy was esophageal stricture in three patients, all of whom were successfully dilated. Sclerotherapy was done under the supervision of a single endoscopist at each hospital.

Death of any cause was considered failure of therapy in both groups. Shunt surgery was also considered a failure when shunt thrombosis developed and sclerotherapy was initiated because clinical circumstances or anatomy precluded further surgery. Sclerotherapy failure was defined as change to surgery necessitated by recurrent hemorrhage despite repeated sclerosis sessions. The decision for surgical intervention was made by the individual gastroenterologist and not based on a specific number or degree of severity of recurrent bleeding episodes.

Pretherapy and Post-therapy Evaluations

All patients had an extensive pretherapy evaluation. In addition to routine post-therapy follow-ups at 3–6-month intervals, comprehensive evaluations were completed at 1 year (shunt = 17; sclerotherapy = 17) and 3 years (shunt = 5; sclerotherapy = 7) after shunt surgery or initiation of sclerotherapy. Patients not seen in person were interviewed by telephone. After August 1984, one of the authors (RAC) returned to Salt Lake City to conduct 1- and 3-year evaluations. One sclerotherapy patient has been lost to follow-up.

Routine clinical and laboratory examinations. Physical examination was directed toward detection of ascites and encephalopathy. Episodes of recurrent hemorrhage, employment status, and presence or absence of continuing alcoholism were recorded. Routine laboratory tests included hematocrit, white blood cell count, platelet count, prothrombin time, partial thromboplastin time, serum albumin, total bilirubin, alkaline phosphatase, AST (SGOT), ALT (SGPT), blood urea nitrogen, and creatinine.

Hepatic hemodynamic variables. Hepatic hemodynamic variables were assessed by visceral angiography, measurement of corrected sinusoidal pressure (CSP), and quantitation of effective hepatic blood flow (EHBF) by a low-dose galactose clearance technique. The portal perfusion grade (PPG) was qualitatively determined from the venous phase of the selective superior mesenteric angiogram (grade 1 = good hepatopetal portal flow to grade 4 = absent flow).[12] Preoperative studies (including left renal vein opacification) also provided essential information about splanchnic venous anatomy, and postoperative angiography determined shunt patency status. CSP was measured as hepatic venous wedge pressure minus free hepatic venous pressure. EHBF was estimated as the infusion rate of low-dose galactose (40–66 mg/min) divided by the steady-state plasma concentration of galactose as described by Henderson et al.[13]

Quantitation of hepatic function. Galactose elimination capacity (GEC) was calculated from serial venous blood samples after a bolus intravenous injection of galactose (500 mg/kg body weight).[14] Removal rate of a 5 mg/kg dose of indocyanine green (ICG) was measured from serial plasma concentrations after intravenous injection.[15] A modified Child's score was derived from serum albumin, total bilirubin, and severity of encephalopathy and ascites (Table 1).[16] Each variable was graded from 1 (best) to 3 (worst) to obtain a total score.

TABLE 1. *Determination of Child's Score*

Points	Albumin (g %)	Bilirubin (mg %)	Encephalopathy	Ascites
1	≥3.5	≤1.5	None	None
2	3.0–3.4	1.6–2.5	Mild	Present
3	<3.0	>2.5	Moderate to severe	Tense

A = 4–5 points, B = 6–7 points, C = 8–12 points.

Psychoneurologic evaluation. An episode of clinical encephalopathy was defined as an incident of mental confusion related by the patient or a family member, or detection of disorientation by a physician. When no precipitating factors were identified, the episode of encephalopathy was considered spontaneous. Induced encephalopathy was defined as mental confusion occurring during gastrointestinal hemorrhage. Disorientation or coma appearing just before death from hepatic failure was excluded. Electroencephalograms (EEG) were graded as normal or abnormal by the criteria of Parsons-Smith.[17] The single psychometric test used was the numbers connection test.[18] Venous blood ammonia was obtained in the fasting state.

Cost analysis. Both initial and total medical costs for each therapy were calculated and compared. Initial medical costs were defined as those incurred during the hospitalization in which shunt surgery was performed or sclerotherapy initiated. Total costs included the initial hospitalization, all subsequent hospitalizations required for treatment of recurrent hemorrhage and complications of therapy or chronic liver disease, and outpatient endoscopic evaluation with or without variceal sclerosis. Only patients from the University of Utah (N = 18) and University of Nebraska (N = 10) were included in the cost analysis; all patients from the Veterans Administration Hospital were excluded.

Statistical analysis. The Kaplan-Meier method was used to plot survival and failure of therapy curves, which were compared by the log rank test.[19] Groups were compared before therapy and at 1 year and 3 years after therapy by chi-square analysis (qualitative variables) and the unpaired t-test (quantitative variables). Serial variables within a group were analyzed by the paired t-test.

Results

Pretherapy Comparison of Shunt and Sclerotherapy Groups

The shunt and sclerotherapy groups were comparable at randomization with respect to cause of cirrhosis, Child's score, quantitative hepatic function and hemodynamic variables, and measurements of neuropsychologic function (Table 2). In addition, all routine blood chemistries, coagulation variables, and hematologic indices were not significantly different between the two

TABLE 2. *Pretherapy Comparison of Shunt and Sclerotherapy Groups*

	Shunt (N = 27)	Sclerotherapy (N = 30)
Alcoholic cirrhosis (%)	81	90
VA patients (%)	48	53
Child's score	6.4 ± 0.4*	6.5 ± 0.3
Bilirubin (mg/dL)	1.9 ± 0.2	1.6 ± 0.2
Albumin (g/dL)	3.3 ± 0.1	3.2 ± 0.1
Encephalopathy (%)	26	30
Ascites (%)	33	47
GEC (mg/min)	271 ± 20	265 ± 16
ICG removal rate (mg/kg/min)	0.21 ± 0.04	0.19 ± 0.03
Hepatic blood flow (mL/min)	1405 ± 79	1314 ± 92
Hepatopetal portal flow (grades 1–3; %)	96	93
Corrected sinusoidal pressure (mmHg)	16.0 ± 1.0	16.6 ± 1.2
Abnormal EEG (%)	33	17
Numbers connection test (sec)	50 ± 4	46 ± 3
Fasting ammonia (μmol/L)	44 ± 5	51 ± 7

* Values expressed as mean ± SEM.

groups. Based on the Child's grading system used, nine shunt (33%) and 10 sclerotherapy patients (33%) were Child's grade C.

Survival

Early mortality (within 1 month of surgery or initiation of sclerotherapy) occurred in one patient in each group. The early postoperative shunt death occurred after an emergency portacaval shunt in a patient who massively rebled after randomization but before elective surgery could be performed. The single early sclerotherapy fatality was secondary to uncontrolled hemorrhage after the first sclerosis session.

Surviving shunt and sclerotherapy patients have been followed up for a mean of 24.4 ± 3.3 and 25.2 ± 3.3 months, respectively. Figure 1 shows Kaplan-Meier survival plots for the two groups as of March 1, 1987. These two curves as well as 2-year survival rates for shunt (65%) and sclerotherapy (61%) groups are not significantly different. Two of four patients in whom sclerotherapy failed who had surgery (splenectomy plus devascularization = 1, interposition mesocaval shunt = 1, end-to-side portacaval shunt = 2) for uncontrolled hemorrhage are still surviving.

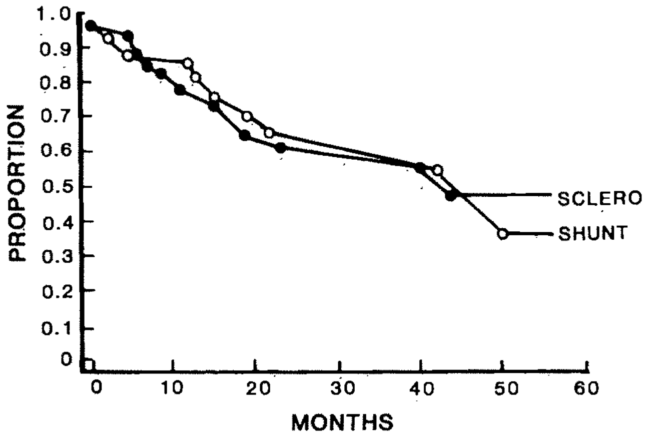

FIG. 1. Kaplan-Meier survival curves for shunt surgery (O) and endoscopic sclerotherapy (●). The curves are not different at any time interval.

The predominant cause of death was different in the sclerotherapy and shunt groups. Eight of the 12 sclerotherapy deaths (67%) resulted from recurrent hemorrhage. Of these eight patients, one died of continuing hemorrhage 5 days after randomization, two died after surgery (2 weeks after mesocaval shunt and 2 years after splenectomy plus devascularization), three died in outlying hospitals more than 300 miles from the tertiary care center, and two died of hepatic failure induced by hemorrhage and were unacceptable candidates for surgery. Six of the eight patients had had endoscopy within the previous month, five bled from gastric varices or portal hypertensive gastropathy rather than from the esophagus, and only one patient was noncompliant. The remaining four sclerotherapy fatalities were secondary to hepatic failure (N = 1), esophageal carcinoma (N = 1), and pneumonia (N = 2). The mean pretherapy Child's score of nonsurviving patients (6.6 ± 0.6) was identical to that of survivors (6.6 ± 0.4).

Six of the 10 shunt deaths (60%) were secondary to hepatic failure. Four of these individuals had resumed heavy alcohol consumption, and the other two had nonalcoholic cirrhosis. Two shunt patients died of recurrent variceal hemorrhage (one after thrombosis of DSRS and one after emergency portacaval shunt for recurrent hemorrhage before elective surgery). The remaining shunt deaths were due to myocardial infarction (N = 1) and ruptured abdominal aortic aneurysm (N = 1). Six of 23 (26%) patients who received the DSRS and three of four (75%) patients with nonselective shunts have died. The mean preoperative Child's score for nonsurviving shunt patients (7.2 ± 0.6) was not significantly higher than for survivors (6.0 ± 0.5).

Failure of Therapy

Failure of therapy (death or change in therapy) curves for the two groups are shown in Figure 2. At no point are the two curves significantly different. Fourteen patients (12 deaths and two survivors of shunt surgery) failed sclerotherapy. Two sclerotherapy patients had surgery and subsequently died. Failure was caused by recurrent hemorrhage in 10 patients (71%). These patients had 8.4

± 1.2 sclerosis sessions and experienced 3.3 ± 0.6 recurrent hemorrhages requiring 5.8 ± 0.7 units of blood per episode. No pretherapy variables significantly separated sclerotherapy successes from failures.

All 10 therapy failures in the shunt group were due to death rather than change of therapy. The single patient who was treated with chronic sclerotherapy after DSRS thrombosis eventually died of recurrent hemorrhage. Early postoperative shunt thrombosis developed in two patients (one DSRS and one interposition portacaval shunt), but both patients were successfully reshunted (one end-to-side portacaval shunt and one interposition portacaval shunt). The overall shunt thrombosis rate was 11%. The only preoperative variable that significantly separated success (survival) from failure (death) in the shunt group was GEC (survivors = 298 ± 26 mg/min, nonsurvivors = 217 ± 20 mg/min; p = 0.05).

Recurrent Hemorrhage

The percentage of patients who rebled, number of rebleeding episodes, and number of units of blood transfusion were all significantly higher in the sclerotherapy group (Table 3). Of the 17 sclerotherapy patients who rebled, 10 (59%) were therapy failures and are discussed above. The remaining seven patients have had either one or two recurrent hemorrhages that have been successfully controlled with sclerotherapy. Most hemorrhages have been documented to be from varices or hypertensive gastropathy by endoscopy; no other lesions have been identified. Pretherapy prothrombin time and partial thromboplastin time were significantly longer (p = 0.05 and p = 0.004, respectively) in sclerotherapy patients who rebled. All other pretherapy variables were similar in patients with and without recurrent hemorrhage.

Three of the five shunt patients who rebled had shunt thrombosis. The remaining two patients had mild recurrent hemorrhage in the early postoperative interval and had patent DSRS by angiography.

Hepatic Function

Neither the quantitative hepatic function tests nor the conventional measures of liver function were significantly different between groups at 1 or 3 years. Likewise, serial GEC, ICG, and Child's score determinations showed no significant changes at 1 year in either group (Table 4). Too few serial measurements have been completed at 3 years for statistical analysis.

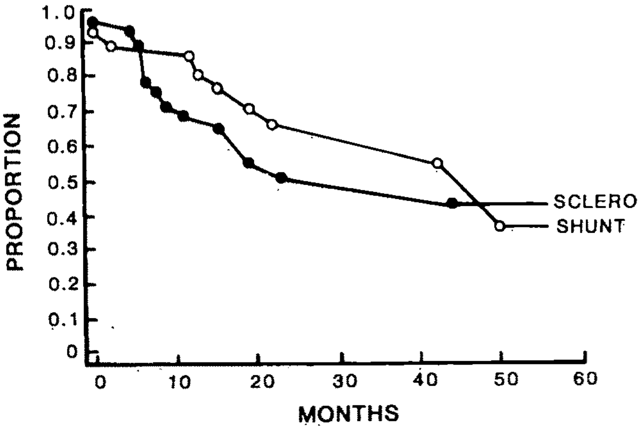

FIG. 2. Kaplan-Meier plots of therapy failure for shunt surgery (O) and endoscopic sclerotherapy (●). The curves are not significantly different at any time interval.

Hepatic Hemodynamic Data

Early postoperative angiography showed preservation of hepatic portal perfusion after 20 of 23 DSRSs and after none of the nonselective shunts. Likewise, corrected sinusoidal pressure (CSP) was maintained in the early postoperative interval after DSRS (preoperative = 15.7 ± 0.9 mmHg, postoperative = 18.0 ± 1.6 mmHg). Analysis of unpaired data at 1 and 3 years showed a significant difference between groups in only CSP at 1 year (shunt = 9.9 ± 1.1 mmHg, sclerotherapy = 16.4 ± 1.8 mmHg; p = 0.01). Serial measurements of EHBF, PPG, and CSP showed a significant change in PPG and CSP in the shunt group at 1 year (Table 5). Four of seven patients who had DSRS and one of eight patients who had sclerotherapy had a worse PPG at 1 year than before therapy (Fig. 3). Since all nonselective shunt patients had lost portal flow immediately after surgery, late postoperative angiograms were not done in these individuals. When nonselective shunt patients surviving at 1 year (shunt group = 3, sclerotherapy group = 2) are considered with DSRS and sclerotherapy patients who had late postoperative angiography, five of 10 shunt patients (50%) and seven of 10 sclerotherapy patients (70%) had evidence of continuing hepatic portal perfusion at 1 year. Two of three angiograms performed at 3 years after DSRS showed hepatopetal portal flow; the single 3-year study in the sclerotherapy group also revealed preservation of portal flow.

Psychoneurologic Function

Four (16%) at-risk shunt patients and two (7%) sclerotherapy patients had at least one episode of spon-

TABLE 3. *Recurrent Hemorrhage*

	Shunt	Sclerotherapy	p
Patients	5 (19%)	17 (57%)	0.003
Episodes	5	48	<0.001
Units of transfusion	28	280	<0.001

TABLE 4. *Serial Hepatic Function and Child's Score*

	Shunt			Sclerotherapy		
	N	Preoperative	1 Year	N	Preoperative	1 Year
Child's score	17	6.5 ± 0.7	5.9 ± 0.5	17	6.7 ± 0.4	5.7 ± 0.4
GEC (mg/min)	11	284 ± 30	279 ± 34	15	261 ± 20	254 ± 19
ICG (mg/kg/min)	10	0.17 ± 0.04	0.17 ± 0.04	15	0.19 ± 0.04	0.20 ± 0.04

taneous encephalopathy during the follow-up interval (Table 6). This complication required hospitalization on four occasions (two patients) in the shunt group and a single hospitalization in the sclerotherapy group. An additional four (14%) sclerotherapy patients had encephalopathy in association with recurrent hemorrhage. Nine shunt (43%) and six sclerotherapy (26%) patients had an abnormal EEG on at least one occasion after initiation of therapy. Overall, there were no differences between groups with respect to clinical, EEG, or psychometric manifestations of post-therapy encephalopathy (Table 6).

Medical Costs

Initial medical costs were significantly higher for shunt patients ($22,473 ± 3521, N = 14) than for sclerotherapy patients ($10,410 ± 1893, N = 14) ($p = 0.007$). However, total medical costs were similar in the two groups (shunt = $34,474 ± 5499; sclerotherapy = $37,648 ± 6392) during a mean follow-up interval of 20 ± 5 and 24 ± 6 months for shunt and sclerotherapy patients, respectively. The higher follow-up costs in the sclerotherapy group were due to the need for serial endoscopies and more frequent hospitalizations (shunt = 16, sclerotherapy = 34) in that group.

Discussion

The major finding of this study is that elective shunt surgery and chronic endoscopic sclerotherapy provide similar long-term survival rates and quality of life for cirrhotic patients who bleed from esophageal varices. The most common causes of death in shunt and sclerotherapy patients were hepatic failure and recurrent hemorrhage, respectively. Despite a comprehensive pretherapy evaluation that included multiple hemodynamic variables and quantitative measures of hepatic function, no test accurately predicted survival in the sclerotherapy group. Although functional hepatic reserve, usually assessed by Child's class, has been a useful prognosticator in some sclerotherapy series,[7,20] pretherapy Child's score was identical in patients who survived and in those who died after endoscopic sclerosis in the current investigation. In contrast, quantitative hepatic function as estimated by GEC predicted survival after shunt surgery. After a 2-year minimum follow-up, five of seven shunt patients with a preoperative GEC less than 250 mg/min have died. Only one patient with a GEC greater than 250 mg/min has died. Although preoperative Child's score was higher (worse hepatic function) in nonsurvivors than in survivors in the shunt group, this difference did not reach statistical significance. These results suggest that chronic sclerotherapy may be preferable to shunt surgery for patients with marginal hepatic reserve.

The 57% of sclerotherapy patients in whom recurrent hemorrhage developed is in the range reported by others.[7,8,20] Ten of the 17 patients with recurrent bleeding had catastrophic hemorrhage, which resulted in death in eight patients. Four of the ten patients had surgery, and two are currently alive. Thus, only two sclerotherapy failures have been salvaged by surgery. Several factors account for this low salvage rate. Recurrent hemorrhage was severe in all of these patients and the location of bleeding in the stomach rather than the esophagus in several individuals prevented temporary

TABLE 5. *Serial Hepatic Hemodynamic Data*

	Shunt			Sclerotherapy		
	N	Preoperative	1 Year	N	Preoperative	1 Year
EHBF (mL/min)	11	1418 ± 109	1191 ± 93	14	1294 ± 112	1155 ± 49
PPG	7	2.0 ± 0.3*	2.6 ± 0.5*	8	1.8 ± 0.4	1.9 ± 0.4
CSP (mmHg)	6	15.3 ± 2.6†	9.7 ± 1.3†	8	13.6 ± 1.8	16.4 ± 1.8

* $p = 0.03$.

† $p = 0.04$.

TABLE 6. *Psychoneurologic Data*

	Shunt		Sclerotherapy	
	Preoperative	Postoperative	Preoperative	Postoperative
Spontaneous encephalopathy (%)	4	16	7	7
Induced encephalopathy (%)	22	0	23	14
Abnormal EEG (%)	33	43	17	26
Numbers connection test (sec)	45 ± 3 (15)	41 ± 2 (15)	47 ± 5 (17)	44 ± 6 (17)
Fasting ammonia (μmol/L)	39 ± 6 (10)	48 ± 7 (10)	50 ± 6 (15)	62 ± 11 (15)

( ) denotes number of patients; paired data before operation to 1 year after operation.

control by balloon tamponade or endoscopic sclerotherapy. In addition, three patients who failed sclerotherapy lived more than 300 miles from the tertiary hospital and bled to death before they could be transported. The three patients who died in our hospitals without surgical intervention had severe hepatic functional decompensation and coma develop secondary to recurrent hemorrhage. These patients were believed to be nonsalvageable, therefore surgery was not performed.

Although a majority of recurrent bleeding episodes (69%) occurred during the first year before variceal eradication was complete in many patients, five of eight fatal hemorrhages occurred in years 2–4, and three of these patients had had prior eradication of esophageal varices. Others[7,8] have also reported recurrent hemorrhage after variceal eradication, confirming the necessity of serial endoscopies in such patients. However, even careful follow-up is no guarantee against fatal hemorrhage as six of the eight patients who bled to death in this series had had endoscopy within 1 month of the fatal episode. Four of these patients had received variceal injections during endoscopy. Because of the frequency and severity of recurrent hemorrhage, pretherapy variables were analyzed to determine if any were predictors of this complication. Only prothrombin time and partial thromboplastin time separated the subgroup that rebled from the subgroup that did not, but the large overlap between subgroups limited the usefulness of these tests for prediction of recurrent hemorrhage.

In addition to prevention of variceal hemorrhage, two objectives of the DSRS are preservation of hepatic portal perfusion and maintenance of portal hypertension. Portal blood contains hepatotrophic hormones essential for maintaining liver size and function and unidentified substances believed to cause encephalopathy when they bypass the liver. Splanchnic venous hypertension may inhibit intestinal absorption of these cerebral toxins.[21] One aim of the current investigation was to determine whether portal flow is more rapidly collateralized after selective variceal decompression (DSRS) than occurs in the natural history of cirrhotic portal hypertension (sclerotherapy group). Both portal flow and CSP were well maintained in the early postoperative studies after DSRS. However, PPG was significantly increased (worsened) 1 year after DSRS, but was unchanged in the sclerotherapy group. Others[22,23] have also reported gradual loss of hepatic portal perfusion during the late postoperative interval after the DSRS, especially in patients with alcoholic cirrhosis. CSP, which reflects portal venous pressure in patients with cirrhosis,[24] was also significantly decreased 1 year after DSRS. Thus far, these late postoperative hemodynamic effects of the DSRS have not translated into major alterations in hepatic or psychoneurologic function. Although a higher percentage of shunt patients have developed spontaneous encephalopathy and abnormal EEGs, the differences between groups are not statistically significant. It is possible that differences in these variables as well as in the quantitative tests of hepatic function may become apparent as the interval of follow-up lengthens.

The results of this study differ from the recently published Emory University trial by Warren and coworkers[20] who reported significantly longer survival and better hepatic function in cirrhotic patients treated by sclerotherapy than for those undergoing elective DSRS.

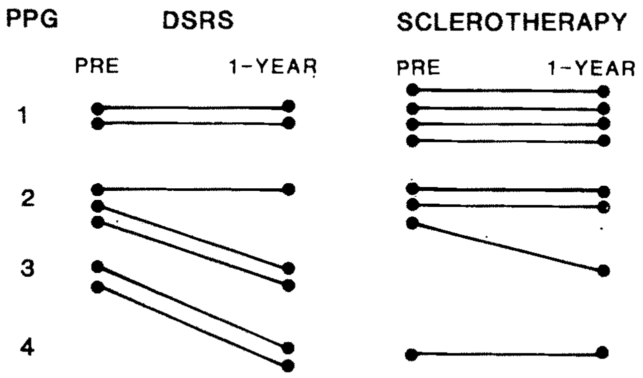

FIG. 3. Angiographic portal perfusion grades (PPG) before and 1 year after DSRS and endoscopic sclerotherapy. The change in PPG is significant after DSRS (p = 0.03) but not after sclerotherapy.

Two-year survival rates for the shunt groups in the two trials are similar (current study, 65%; Emory trial, 59%). In contrast, survival at 2 years after initiation of sclerotherapy in the Emory trial (84%) was greater than for our sclerotherapy group (61%). The major difference between the two investigations is the greater success of the Emory group in salvaging sclerotherapy failures by shunt surgery. At the time of their report, 11 sclerotherapy patients (31%) had undergone surgery and eight (22%) were still surviving. Only four patients (13%) in our sclerotherapy group received surgery and two (7%) are currently alive. Our inability to salvage more sclerotherapy failures was due to generally catastrophic recurrent hemorrhage, often during the first episode, which led to rapid deterioration of hepatic function.

Although the designs of these two trials are similar, several subtle differences may account for the conflicting results observed. First, the patient populations are different. The current investigation contains higher percentages of alcoholic cirrhotics (86% *vs.* 61%) and Veterans Administration Hospital patients (51% *vs.* 0). Although Warren and co-workers[20] reported a higher percentage of Child's C patients than in the current study (44% *vs.* 33%), the methods of classifying patients differ. Analysis of pretherapy data from the two investigations shows higher mean bilirubin and lower mean albumin and GEC in our trial, suggesting inclusion of patients with more advanced hepatic dysfunction. Only patients acceptable for the DSRS (hepatopetal portal flow and manageable ascites) were entered into the Emory trial. We accepted all patients who could undergo any type of shunt, although only three patients had spontaneous reversal of portal flow on pretherapy angiography and 85% of patients in the shunt group received the DSRS. Finally, in the current study, a significant percentage of patients (including three sclerotherapy failures) had to travel over 300 miles to return to the tertiary hospital because of the relatively sparse population and large geographic area of the Intermountain West and Plains compared with the Southeast. Thus, shunt surgery may be preferable to chronic sclerotherapy for patients living in such remote areas. Although it cannot be determined whether these factors account for the differences in results, they should be considered when interpreting the data from the two trials.

The only other study[25] that has compared shunt surgery and sclerotherapy comprised exclusively Child's C cirrhotic patients who were receiving emergency therapy for acutely bleeding varices. Therefore, it is not directly comparable to either the current investigation or the Emory trial.[20] This report by Cello and co-workers[25] showed similar short- and long-term survival rates for portacaval shunt and sclerotherapy patients. As in the current trial, recurrent hemorrhage was significantly more common in the sclerotherapy group and total medical costs were similar for both therapies, even though shunt surgery was significantly more expensive during the initial hospitalization.

In summary, at a mean follow-up interval of 2 years, this randomized trial has shown similar survival rates, levels of hepatic and neuropsychologic function, and total medical costs after shunt surgery (85% DSRS) and chronic endoscopic sclerotherapy. Hepatic portal perfusion and portal pressure were better maintained after sclerotherapy, but this hemodynamic advantage has not yet resulted in a differential in hepatic function between groups. Recurrent hemorrhage was more frequent after sclerotherapy (57%) and was the most common cause of therapy failure. Because of the severity of recurrent bleeding and geographic distribution of patients, only two of 10 sclerotherapy failures have been salvaged by surgery. Although none of the pretherapy variables predicted failure of sclerotherapy, preoperative GEC was significantly higher in shunt survivors than in nonsurvivors, suggesting that patients with limited hepatic functional reserve might be better served by sclerotherapy than by shunt.

Acknowledgments

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Discussion

DR. LOUIS R. M. DEL GUERCIO (New York, New York): I am filled with admiration for the authors' ability to perform this difficult piece of work in such a fine fashion. Those who deal with these types of patients know how difficult it is to maintain such controls.

I rise simply to speak about the patients who fail sclerotherapy. Sclerotherapy can be compared with the little girl with the curl in the middle of her forehead. When it's good, it's very, very good, and when it's bad, it's terrible. The question is what to do with the sclerotherapy failures.

The authors point out that they could salvage only 20% of these sclerotherapy failures, that is, those who continue to bleed despite attempts at sclerotherapy.

(Slide) We have been very concerned with this because at our institution, the Westchester County Medical Center, most bleeding cirrhotics who are referred to us are sclerotherapy failures.

What we do is a combination of splenic artery embolization through the standard Seldinger approach, putting Gianturco coils in the splenic artery to reduce the splenic contribution to portal flow and to reduce the degree of secondary hypersplenism with improvement in platelet counts.

The second part of the procedure is performed through a minilaparotomy in the x-ray suite under local anesthesia. We cannulate a branch of the mesenteric vein, go up into the portal system, and internally sclerose the coronary collaterals to the varices with absolute alcohol and use Gianturco coils to plug off the collaterals. In other words, this is a nonoperative Sugiura operation.

(Slide) In 36 consecutive patients (no one excluded) who were sclerotherapy failures, all of the Class B patients survived for at least 1 year. The red shows the survival of the Class C cirrhotics where 60% survived for at least 1 year, and the combination of Bs and Cs had an even better survival.

This is a satisfactory alternative to shunt surgery and can be done expeditiously in the x-ray department.

My question to the authors is: what are their plans in terms of better management of the sclerotherapy failures?

DR. JOHN PHILIP SANDBLOM (Sweden): I first express great happiness in having survived to be able to attend once more the summit of the surgical year, the meeting of the American Surgical Association! This gives me the opportunity to discuss one of the great interests in my surgical life with this excellent presentation of comparing shunt and sclerotherapy in portal hypertension.

My experience is long; it started 40 years ago and we once had one of the largest series of shunt operations in the world. I have always advocated the shunts for portal hypertension, although during recent years less successfully, as these have been in less favor. I am therefore very pleased to have this judged objectively with a prospective study, to see that the two methods are equal in many respects, and that we shall be able to continue doing the shunts with good prospects.

There are two more benefits from normalization of the portal pressure. Firstly, it corrects the stasis in the splanchnic tissues, for example in the gastric mucosa where erosive gastritis often ensues. Secondly, it relieves the patients of the great danger of severe hemorrhage after abdominal trauma or abdominal operations. I have once seen a patient with portal hypertension die of hemorrhage during a simple cholecystectomy.

In our series we had several cases of biliary cirrhosis due to ascending cholangitis from biliodigestive shunts. These patients often need reoperations for correction of anastomotic strictures.

In the first case we had great difficulties with hemorrhage. In the three remaining cases, we performed the operation in two stages: first the shunt operation and then when the portal pressure had been reduced to normal, with hemostasis.

I ask the authors if they have any experience with the advantage of normalizing the portal pressure in these cases.

DR. J. MICHAEL HENDERSON (Atlanta, Georgia): I congratulate Dr. Rikkers for putting surgical decompression and endoscopic sclerosis of varices to the true test of a prospective randomized clinical trial. In a similar trial at Emory our data look different.

My main area of discussion will focus on failures of sclerotherapy. In our study, 16 of 37 patients randomized to sclerotherapy either died or failed that therapy: four patients had their bleeding controlled, but have died of hepatic failure, one patient in this group has died of bleeding, which is in marked contrast to Dr. Rikkers' study, the other 11 patients had recurrent bleeding severe enough to be considered sclerotherapy failures and crossed over to shunt surgery. There was no operative mortality in these 11 cross-over patients, but four have subsequently died of hepatic failure at 3–47 months after cross-over.

The second major difference in the results of our two studies lies in the effect of therapy on liver function. At randomization, the severity of liver disease appears similar in the two studies. Our study, in contrast to Dr. Rikkers', showed significant improvement in hepatocyte function in the sclerotherapy group over time. Improvement in the galactose elimination capacity occurred predominantly in alcoholic cirrhosis patients, in whom frequent return for sclerotherapy may have been an added incentive to stop drinking.

These two factors, the ability to surgically salvage sclerotherapy rebleeding failures, and improved hepatic function in the sclerotherapy group, combine in our study to give significantly improved survival to that group. The survival curve of our shunt group is similar to Dr. Rikkers' survival curves for both his groups, but at all time points the survival curve of our sclerotherapy group is significantly ($p < 0.03$) better than our shunt group. At a median 3.5-year follow-up, the sclerosis group, with surgical salvage of 30% of the patients, has a significantly better outcome. Our study supports an approach of initial sclerotherapy for all patients, which allows time to define their liver disease and its course. Failures from rebleeding or progressive liver disease can then be rationally referred for further therapy by shunt surgery or transplantation as appropriate.

I ask two questions: first, sclerotherapy is a viable treatment for some patients. Has it altered how you advise your patients outside the confines of your randomized study? Second, what are the key factors in sclerotherapy rebleeding? Is it access to the therapy? Is it technique? Or is it patient population?

DR. IWATSUKI (Pittsburgh, Pennsylvania): I also compliment Dr. Rikkers and his colleagues on their well-designed clinical study. We have been interested for some time in treating variceal bleeding of far-advanced cirrhosis by radical portal decompression through a normal liver graft, or to put it more plainly, with orthotopic liver transplantation.

I present our preliminary results of liver transplantation for bleeding esophageal varices in far-advanced cirrhosis.

(Slide) Among 500 consecutive patients who received liver transplantation under cyclosporine and steroid therapy, more than 1.5 years ago, 136 patients had had definite history of bleeding from esophageal varices. All 136 patients were classified in Child's C or an even worse category.

The 1-year actual survival rate after transplantation was 80% and the 3- and the 5-year actuarial survival rates were 73% and 70%, respectively.

(Slide) The survival rates of patients with far-advanced cirrhosis or Child's class C were vastly different after liver transplantation than those after Dr. Warren's selective shunt, sclerotherapy, Sugiura-type nonshunt procedures, or nonselective portacaval shunt.

In this context Dr. Rikkers' paper is unusually important. He has shown that survival with conservative sclerotherapy is the same as with the best of the shunting procedures.

If this is true, and I believe it is, almost all such shunt operations that greatly complicate the next and the final step of transplantation are going to be abandoned except under the most unusual circumstances.

I ask Dr. Rikkers one question. What is your choice of treatment for bleeding varices on the patients with far-advanced Child's Class C cirrhosis at your institution, now that you have liver transplantation capabilities in Omaha?

DR. MARSHALL J. ORLOFF (San Diego, California): I rise to make three observations about this interesting study by Dr. Rikkers and his colleagues and to briefly describe our recent results that differ substantially from those he has presented.

Firstly, the study that we have just heard involved highly selected patients subjected to elective treatment. Therefore, it dealt with only a portion of the bleeding cirrhotic population, and the conclusions do not apply to all patients who come to the emergency room with bleeding varices.

Secondly, 19% of the patients who had elective shunt rebled, which I believe is quite high. Whenever a shunted patient rebleeds, it represents a failure of the operation.

Thirdly, I must confess to a bit of disappointment in the 2-year survival rate of 65% for elective shunt in selected patients.

(Slide) In 1983, our gastroenterology division performed a prospective evaluation of endoscopic sclerotherapy in unselected cirrhotic patients with bleeding varices. Each patient who entered the medical service for 3 years, all comers included, had emergency endoscopic sclerotherapy and then repetitive long-term sclerotherapy (as many as 17 sessions with an average similar to that of Dr. Rikkers' group of 7 sessions per patient).

The study involved 53 consecutive cirrhotics. Eighty-nine per cent rebled from varices after their final sclerotherapy session. A mean of 16.3 units of blood transfusion was required during the initial hospitalization.

Eleven patients ultimately had a portocaval shunt because of uncontrollable bleeding, and I might say that they made up many of the 2-year survivors.

(Slide) Seventy per cent of the patients survived to leave the hospital after the initial bleeding episode, but almost all of them were soon readmitted because of rebleeding.

As of 1986, 33% of these unselected patients were alive and the 2-year survival rate was only 17%.

The differences are striking when the results of endoscopic sclerotherapy at our institution are compared with our results of the emergency direct portocaval shunt done within 8 hours of admission in 84 unselected patients from 1977–1982.

Rebleeding occurred in 2% of the emergency shunt patients *versus* 89% of the sclerotherapy patients.

The emergency shunt patients required 0.5 units less of transfused blood than the sclerotherapy patients, and 2-year survival was almost 5 times greater in the emergency shunt group than in the sclerotherapy group.

(Slide) At the AGA meeting last year, we reported the results of a soon to be published prospective, randomized comparison of emergency portocaval shunt and emergency medical therapy followed by elective shunt in unselected patients. Emergency shunt resulted in significantly greater early and long-term survival than emergency medical therapy followed by elective shunt. (Slide) The higher survival rate with emergency shunt was particularly striking in patients with Child's group B, 100% compared with 33%, and Group C, 64% compared with 14%.

This slide compares the 5-year survival curves obtained in our various studies in unselected patients. The survival rates in the two emergency shunt groups, randomized and unrandomized, were similar and were much greater than the survival rate in the randomized medically treated patients followed by elective shunt.

I must point out that the 2-year survival rate of 79% after emergency shunt in unselected patients is greater than the 65% reported by Dr. Rikkers after elective shunt in selected patients.

DR. RAPHAEL S. CHUNG (Syracuse, New York): Unlike shunt surgery, the failure of sclerotherapy is not well known. Failure of a shunt is documented by occlusion, but not many people, especially those who are not endoscopists, know what is the exact cause for recurrent bleeding after sclerotherapy.

One of the puzzling conditions to treat is recurrent bleeding after deep ulcerations in the musculature after sclerotherapy, which is a complication of overzealous treatment because the collaterals in the muscles are eroded and being hypertensive, they tend to bleed persistently.

I ask Dr. Rikkers if any of the patients who had recurrent bleeding from sclerotherapy were bleeding from deep ulcerations and also how many patients in the series developed esophageal strictures? Both of these serve as a rough indication of the quality of the technique of sclerotherapy.

DR. LAYTON RIKKERS (Closing discussion): I thank the discussants for their questions and comments.

Dr. Del Guercio had better results than we have had in salvaging sclerotherapy failures. Only 30% of our sclerotherapy failures were successfully salvaged by surgery and one of these patients died 2 years later. A major cause of the low salvage rate of sclerotherapy failures in our study is the wide geographic distribution of the patients. Several patients died in outlying hospitals and others had advanced hepatic and neuropsychological dysfunction develop by the time of transfer and were no longer salvageable by surgery. These results suggest that shunt surgery may be preferable for patients living in remote areas.

Dr. Sandblom, I do not have experience with portal decompressive procedures before complex biliary surgery in patients with portal hypertension.

Dr. Henderson, our trial and the Emory trial are similar, but there are several important differences that may account for the variance in results. First, the Emory trial compared only the distal splenorenal shunt with sclerotherapy. Therefore, patients with contraindications to the distal shunt, *e.g.*, medically intractable ascites, were presumably excluded. Since nonselective shunts were included in the surgical arm of our study, such patients could be entered. Second, our trial contained a higher percentage of alcoholic cirrhotics and also included VA patients. In addition, we accepted patients within a geographic radius of 500 miles. The Emory trial excluded patients who lived more than 200 miles from Emory University Hospital. The potential importance of geographic distribution has been alluded to already. Finally, there are many ways of categorizing patients by Child's classification. Although the authors of the Emory trial report that 44% of patients were Child's class C compared with 33% of C patients in our trial, a direct comparison of data from the two trials shows that both serum albumin and galactose elimination capacity were significantly lower in our patients. Therefore, it appears that our trial consisted of possibly less compliant patients with more advanced liver disease who lived within a larger geographic area than the patients in the Emory study. It is likely that these factors account for the poorer survival of sclerotherapy patients in our trial.

Dr. Iwatsuki presented impressive results following liver transplantation for variceal hemorrhage. During the past 1.5 years, we have done 90 liver transplants at the University of Nebraska. We also prefer liver transplantation to portal decompression or sclerotherapy for Child's C patients with nonalcoholic cirrhosis who are in the appropriate age range. Unfortunately, few alcoholic cirrhotics are liver transplantation candidates and, therefore, continue to be available for entry into our trial.

Dr. Orloff, our objective was to look at the elective rather than the emergency management of patients with variceal hemorrhage. We have found that a combination of vasopressin, balloon tamponade, and acute sclerotherapy controls hemorrhage in greater than 85% of acutely bleeding patients. Emergency surgery is considered only when these measures fail.

The 19% rebleeding rate in the shunt group includes three patients with thrombosis, two of whom were successfully reshunted, and two patients with patent distal splenorenal shunts who had minor bleeding episodes confined to the early postoperative interval.

I admire Dr. Orloff's salvage rate in his emergency shunt series. However, I believe it is fair to say that no one else has approached his results with emergency shunts.

Dr. Chung, our sclerotherapy failures did not bleed from esophageal ulcers. Rather, they bled from the stomach either from gastric varices or from portal hypertensive gastropathy, which we find to be major consequences of sclerotherapy. The only notable complication of sclerotherapy was esophageal stricture, which developed in three patients. All of these strictures were successfully dilated without surgical intervention.

Evolving Strategies for the Repair of Complex Renovascular Lesions

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Fifty-five patients with 59 complex renovascular lesions required two or more branch artery anastomoses during aortorenal grafting. Forty-five reconstructions involving 112 branches were facilitated using hypothermic *ex vivo* perfusion preservation, whereas 14 involving 28 branches were repaired *in situ*. *Ex vivo* repair was used whenever the kidney was considered unreconstructable by *in situ* techniques. Fibromuscular dysplasia predominated and the branched internal iliac artery was used for renal artery substitution. There were no deaths and only one kidney (*ex vivo*) was lost. Branch vessel occlusion occurred in two of 140 anastomoses (1.4%). Ninety-eight per cent (51/52) of the heparinized patients had cure or improvement at mean follow-up of 5 years. No late graft dysfunction occurred in postoperative angiographic follow-up. The branched internal iliac artery is uniquely suited and remains the preference of the authors for the replacement of the diseased renal artery and its branches. The *in situ* repair is ideally suited for lesions limited to the renal artery bifurcation. *Ex vivo* repair is reserved for complex or reoperative distal arterial lesions. Unique characteristics in the group include: bilateral lesions (25%), solitary kidney (22%), reoperative lesions (16%), children (9%), and coexisting significant aortic disease (7%). *In situ* and *ex vivo* repair meet all the challenges of complex renovascular disease. The strategies outlined will achieve outstanding long-term total and segmental renal salvage in the treatment of hypertension or aneurysmal disease. When *ex vivo* repair is required, it can be accomplished with only one additional simple maneuver, the reanastomosis of the renal vein.

THE COMBINATION OF the arterial autograft, temporary hypothermic kidney perfusion, and microvascular branch renal artery repair[1,2] was the basis for the original report on *ex vivo* renal artery reconstruction more than a decade ago.[3] Ongoing experience salvaging kidneys threatened by complex lesions of the distal renal vasculature has convinced us of the validity of this operative approach and better defined its application.[2,4]

This report analyses the results of 55 patients requiring extensive surgical reconstruction of a wide spectrum of challenging lesions of the distal renal artery and its branches. Not all distal renal artery lesions have required *ex vivo* repair, and we now selectively perform *in situ* renal artery replacement when lesions are confined to the primary renal bifurcation. A review of our experience has evolved a strategy that allows both anatomic and functional reconstruction of a normal renal arterial system with consistent kidney salvage and amelioration of hypertension.

Clinical Material

Among 135 patients who had iliac artery autograft reconstruction for significant renovascular lesions between 1964 and 1986, 55 patients (40%) required multiple branch arterial repair because of the distal extent of their lesions and represent the case material for this study (Table 1). There were 50 females (92%) and five males (8%) with a mean age of 40.1 years (range: 12–68 years).

In 52 procedures (12 *in situ*, 40 *ex vivo*) (89%), the indication for renal revascularization was diastolic hypertension, with a mean duration of 6 years. Six patients had renal artery aneurysms (2 *in situ*, 4 *ex vivo*) (10%). In the remaining patient, a kidney harvested for transplant was discovered unexpectedly to have fibromuscular dysplasia. The considerable majority of patients (85%) had normal serum creatinine levels before operation. However, two patients who had *in situ* procedures and six patients who had *ex vivo* procedures had evi-

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dence of impaired renal function before surgery (serum creatinine level ≥ 1.3 mg/dL).

Fourteen reconstructions (14 patients, 17 kidneys) were performed *in situ,* whereas 45 renal artery repairs (41 patients, 45 kidneys) required the *ex vivo* technique. All *in situ* repairs involved two renal artery branches. *Ex vivo* repairs involved two branches in 24 patients, three branches in 11 patients, and four branches in seven patients. Three *ex vivo* repairs in reoperative cases involved only the main renal artery or one branch. The mean number of branches repaired in *ex vivo* procedures was 2.5.

Twenty-six patients (47%) had total renal parenchymal revascularization. Solitary kidneys were revascularized in 12 patients (3 *in situ,* 9 *ex vivo*) (22%). Bilateral renal reconstruction was performed in 14 patients (25%) (staged in 5 patients and simultaneous in 9 patients). Three patients had bilateral *in situ* repairs, two had bilateral *ex vivo* repairs, and two had one *in situ* and one *ex vivo* repair each. The remaining seven patients had *ex vivo* repair on one side and contralateral *nonbranched in situ* repair. These seven nonbranched repairs are not discussed in this report. Nine cases were reoperative (1 *in situ,* 8 *ex vivo*) and five were performed in children (2 *in situ,* 3 *ex vivo*). Only four patients required concomitant aortic reconstruction.

Although selective traditional screening tests were used, the intravenous pyelogram (21 of 28 positive, 75%) and renal vein renin determinations (20 of 23 positive, 87%) were helpful but not absolute indicators of renovascular hypertension. Aortography, supplemented by selective renal arteriography with magnification and multiple views, reliably defined these distal patterns of branch vessel disease.

TABLE 1. *Clinical Material*

Technique	No. of Patients	Kidneys	Branches	Indication	
				Hypertension	Aneurysm
In situ	14	17	28	12	2
Ex vivo	41	45	112	40	4
Total	55	62	140	52	6

Technique

A midline abdominal incision was routinely used for both *in situ* and *ex vivo* repair. Retroperitoneal exposure of the aorta and renal arteries was accomplished through the retroperitoneal midline for *in situ* bifurcation repairs. *Ex vivo* repairs were facilitated by medial reflection of the ascending or descending colon. This gave full exposure of the kidney, the course of the ureter, and the ipsilateral iliac arterial system. Circumferential mobilization of the pararenal aorta, involved renal artery, and accompanying vein were accomplished. The hypogastric artery was mobilized from its origin to its second or third order branches depending on the type of renal replacement required, but was not harvested until the time for grafting. For *ex vivo* reconstruction, after opening of Gerota's fascia, the kidney was fully mobilized, together with the ureter and its accompanying vasculature, down to the level of the pelvic brim. This allowed the kidney to be conveniently perfused on a lower abdominal platform without dividing the ureter.

In Situ *Reconstruction*

A previous report[5] described this technique, which requires a short interval of total aortic occlusion. The segment of aorta chosen for the origin of the autograft is immediately inferior to the origin of the diseased renal artery. Total rather than partial aortic occlusion facilitates placing the circular aortotomy for the proximal anastomosis in a posterolateral position. This aortotomy should match the diameter of the proximal end of the hypogastric artery. The anastomosis is performed with interrupted sutures of fine silk. The superior renal artery branch is ligated at the distal extent of the disease, and the branch vessel beyond that point controlled with a fine vascular clamp. This branch is then transected, gently dilated, and anastomosed to the superior autograft branch with interrupted fine sutures. Flow is restored to the renal parenchyma supplied by this branch through the autograft while the inferior renal artery branch is transposed to an autograft branch in an identical manner. The excluded diseased renal artery is then resected for pathologic examination. The mean renal ischemia time for *in situ* repair was 42.6 minutes (range: 16–102 minutes).

Ex Vivo *Reconstruction*

After extensive mobilization of the renal vessels from their junction with the vena cava and aorta to the renal hilus, the kidney and ureter are freed. The renal artery and vein are controlled with vascular clamps and then transected, and the kidney is positioned on the lower anterior abdominal wall. A tourniquet is placed securely around the ureter to prevent collateral flow into the kidney during the *ex vivo* perfusion. Ringer's lactate solution at 4 C is flushed through the renal artery until the venous effluent is clear. The renal artery is cannulated and then connected to the perfusion manifold of the dissecting platform located on the lower abdominal wall. Hypothermic perfusion is begun and the kidney maintained at about 8–12 C. Thorough dissection of the renal artery branches and vein is possible far into the hilus, to a level distal to visible and palpable disease (Fig. 1). The skeletonized distal renal artery and its branches are now ready for replacement.

The arterial autograft is now harvested, its lumen irrigated with heparinized saline solution, and its configuration studied to match that of the renal arterial tree to be

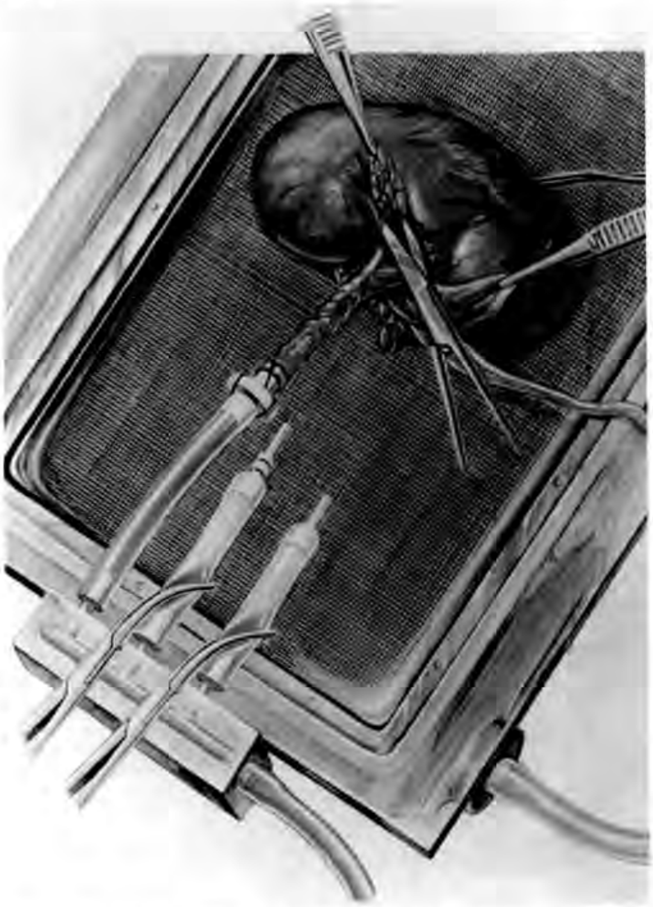


FIG. 1. Extended dissection of renal hilus being performed with hypothermic perfusion through the diseased native renal artery. Note intact ureter and additional cannulae, to which the autograft will be attached.

replaced. Sequential branch anastomosis allows segmental transfer of the circulation from the diseased native renal artery and its branches, under perfusion, to the hypogastric artery substitute, which is connected to another port on the perfusion manifold. Segmental renal ischemia averages 15 minutes for each of the two, three, or four vessels to be anastomosed. The hypothermic perfusion is therefore nearly continuous and maintains a surface temperature of between 8 and 12 C. Interrupted 6-0 or 7-0 Tycron sutures are used for the anastomoses. Vessels under 2 mm in diameter are anastomosed over a metal dilator stent to allow precise end-to-end approximations and to prevent anastomotic narrowing.

The reconstructed renal artery tree is examined for leakage by temporarily elevating the perfusion pressure to the patient's systolic pressure. If identified, these can be easily and precisely repaired. The perfusion pressure is returned to a lower level for an additional 10 minutes to ensure maximum renal hypothermia before reimplantation. The kidney is placed in the renal fossa and the artery is attached first to the posterolateral circular aortotomy, using the technique previously described for *in situ* repair. The renal vein is reattached to the native renal vein (left side) or to an elliptical cavotomy (right side) using continuous suture technique. The venous and arterial clamps are now removed restoring the renal circulation. The mean perfusion time for *ex vivo* repairs was 94.3 minutes (range: 57–160 minutes), whereas the mean warm renal ischemia time was 57.8 minutes (range: 21–91 minutes).

Results

There were no deaths in this patient group. Significant nonrenal morbidity occurred in seven patients (12%), and was major in three (requiring reoperation) and minor in four. Intraoperative (2) and postoperative (2) graft occlusion occurred in four patients (5 kidneys), three in the *in situ* group and one in the *ex vivo* group. The *ex vivo* kidney was lost, whereas all four *in situ* kidneys were salvaged. Postoperative branch occlusion occurred in only two branches, both in kidneys reconstructed using the *ex vivo* technique. No patient required dialysis. Seven patients who had *ex vivo* procedures demonstrated a transient decline in renal function after operation, which had resolved at the time of discharge (Table 2). Three patients who had *in situ* procedures had a similar decline in function, but *did not* recover their preoperative level of function before the time of discharge. Follow-up renal scans revealed no kidney to manifest acute tubular necrosis.

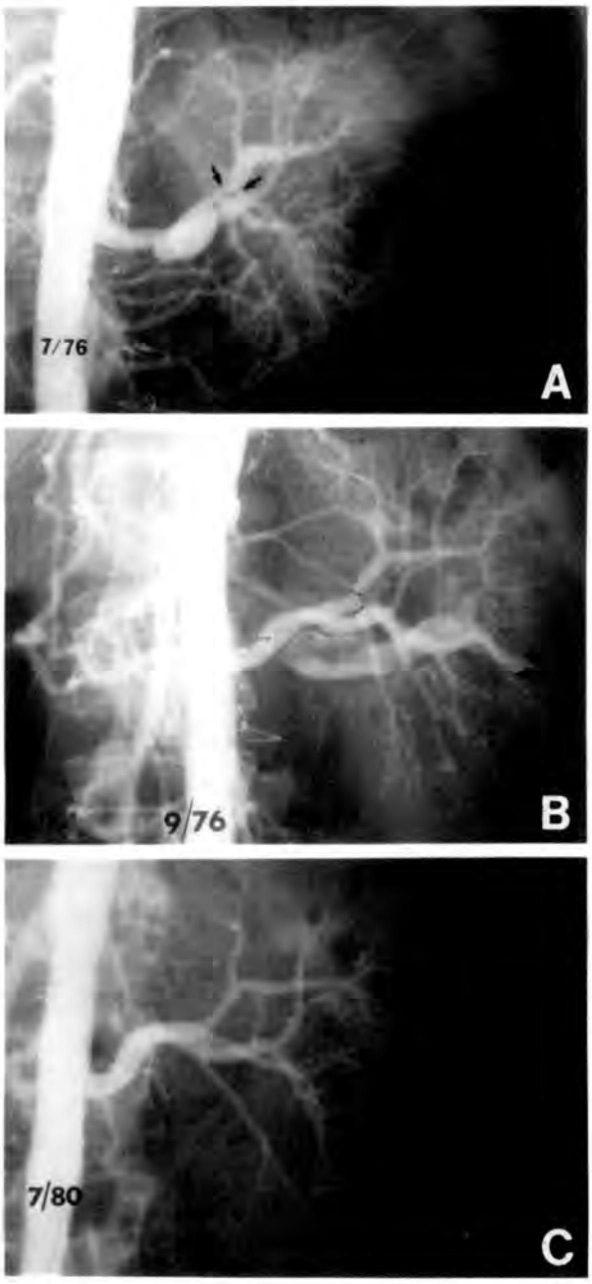
Among the 52 patients who had diastolic hypertension, at discharge all patients were either cured or improved. Late follow-up, obtained at a mean interval of

TABLE 2. *Results*

	Renal Function		Hypertension			
	Postoperative		Postoperative		Late Follow-up	
	In situ	*Ex vivo*	*In situ*	*Ex vivo*	*In situ*	*Ex vivo*
Cured	—	—	11	34	10	31
Improved	0	3	1	6	2	8
Unchanged	11	34	0	0	0	0
Worse						
Transient	0	7	0	0	0	1
Persistent	3	0	0	0	0	0
Unknown	—	1	—	—	—	—

76 months (range: 1–168 months), showed that 51 of 52 patients (98%) remained either cured or improved (Table 2). The one patient who was worse at follow-up was the patient who lost her kidney.

Late arteriographic assessment was performed in 24 patients (44%) at a mean time of 40.6 months after operation (range: 1–122 months). Stable graft configuration was demonstrated in all patients, without graft degeneration or stenosis (Figs. 2 and 3).



FIGS. 2A–C. *A*. Aneurysmal deterioration of a vein patch angioplasty used to incompletely treat extensive fibromuscular dysplasia in a solitary kidney. Note significant disease involving branches distal to the patch (arrows). *B*. Postoperative study after *ex vivo* repair. Arteriovenous fistula is secondary to a percutaneous renal biopsy. *C*. Late follow-up study shows normal-appearing renal architecture.

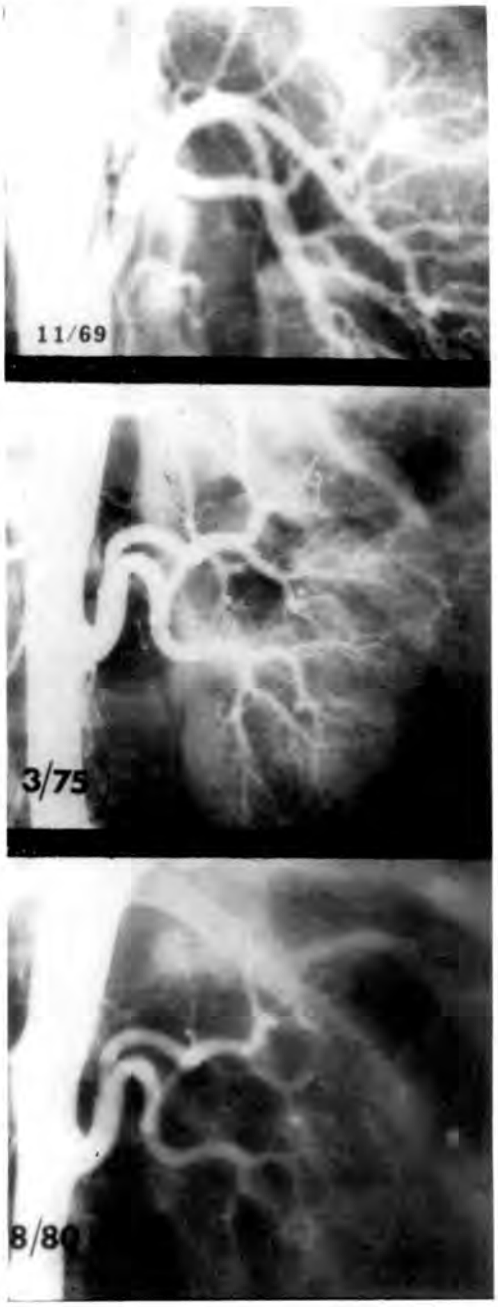


FIG. 3. Serial arteriograms obtained 6 and 11 years after *in situ* branched renal artery. Note preservation of normal renal anatomy.

Indications for *Ex Vivo* Repair

Various factors, alone or in combination, favor *ex vivo* renal artery reconstruction over *in situ* repair. The two basic principles of the successful management of these complex distal lesions are: (1) uncompromised exposure must be provided to get beyond the disease limits, and (2) adequate time must be taken to perform the meticulous repair without unduly risking renal function. Certain circumstances tend to impede either or both of these requirements.

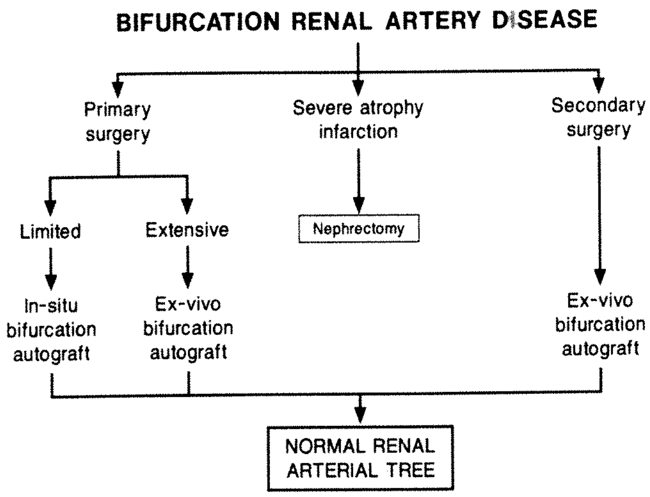

BIFURCATION RENAL ARTERY DISEASE
Primary surgery
Severe atrophy infarction
Secondary surgery
Limited
Extensive
Nephrectomy
In-situ bifurcation autograft
Ex-vivo bifurcation autograft
Ex-vivo bifurcation autograft
NORMAL RENAL ARTERIAL TREE

FIG. 4. Schematic approach to bifurcation renal artery disease.

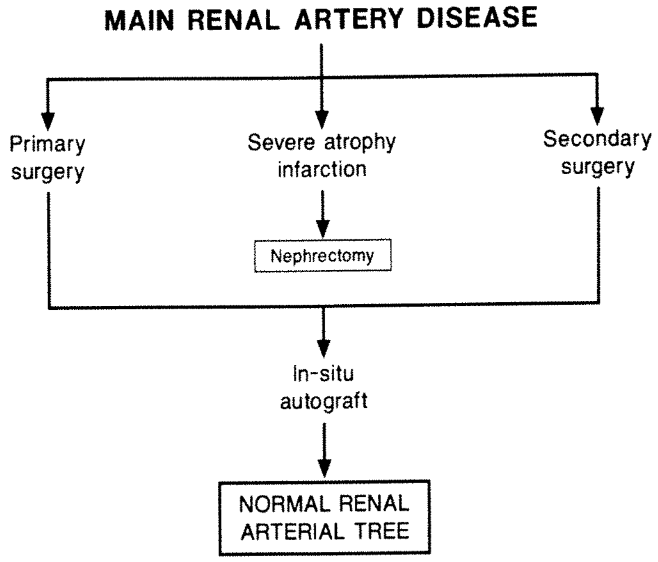

MAIN RENAL ARTERY DISEASE
Primary surgery
Severe atrophy infarction
Secondary surgery
Nephrectomy
In-situ autograft
NORMAL RENAL ARTERIAL TREE

FIG. 6. Schematic approach to main renal artery diseases.

Extent of Disease

Fibromuscular disease, aneurysmal disease, and spontaneous dissection commonly involve the renal arterial tree beyond the primary and even secondary branch points. At each branch point there is a rapid reduction in renal artery size. In addition, in the renal hilus there is a close relationship of arterial, venous, and collecting system structures. Unobstructed exposure is necessary to allow safe performance of the extensive dissection, precise identification of the involved segments, and meticulous arterial repair, which are necessary to construct a normal renal artery. Therefore, only if the lesion is limited in extent and located solely in the primary renal bifurcation, can an *in situ* repair be performed safely (Fig. 4). If primary bifurcation disease is extensive or if multiple renal artery branches are involved, then *ex vivo* reconstruction is necessary (Figs. 4 and 5).

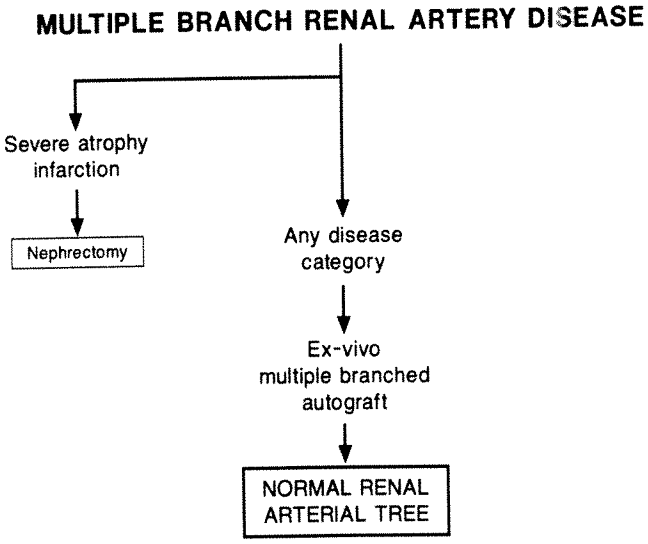

MULTIPLE BRANCH RENAL ARTERY DISEASE
Severe atrophy infarction
Nephrectomy
Any disease category
Ex-vivo multiple branched autograft
NORMAL RENAL ARTERIAL TREE

FIG. 5. Schematic approach to disease involving multiple distal branches.

Reoperative Renal Reconstructions

When a primary renal artery reconstruction has failed because of significant residual lesion, degeneration of the repair (Fig. 2A), or progression of previously insignificant distal disease, reoperation is warranted. If the procedure will involve the main renal artery only, this can usually be successfully approached *in situ* (Fig. 6). However, if the repair will require reconstruction of the primary bifurcation or more distal segments of the renal arterial tree, then the *ex vivo* technique is necessary (Figs. 4 and 5). Previously, these circumstances often led to nephrectomy. Currently, the *ex vivo* approach makes renal salvage feasible for these technically difficult and challenging procedures. Among our nine patients who had reoperation, eight had *ex vivo* repair and transient renal dysfunction followed in three cases. Only seven of 49 primary operations were followed by renal function decline, but in three of these cases it was persistent at discharge. Thus it seems that reoperation is associated with a higher risk of renal injury, and the protection offered by *ex vivo* repair with cold perfusion is important in minimizing at least the severity if not the actual incidence of the renal injury.

Solitary Kidney

A solitary kidney affected with distal disease may have anatomy appropriate for the *in situ* technique. However, the *ex vivo* technique offers a higher degree of safety in reducing significant renal parenchymal injury. Not uncommonly a patient with a solitary kidney already has a measurable degree of impaired renal function, as was the case with five of the 12 patients with solitary kidneys in this study. Not surprisingly, then, 50% of patients (6 of 12) with solitary kidneys had some renal function decline after repair, compared with only 9% of patients (4 of 46) with two kidneys, even though nine of these patients had simultaneous bilateral renal revascularization. Among patients who had *ex vivo* procedures and had solitary kidneys, renal function change was transient, whereas among patients who had *in situ* procedures it was persistent at discharge. We conclude that when the patient does not have the luxury of contralateral renal function, there is a significant risk of repair-associated renal injury and the *ex vivo* technique is safer both in terms of immediate and long-term results.

Discussion

The past three decades have seen an evolution of techniques for renal artery reconstruction: patch angioplasty, bypass, or replacement grafting are the options available for lesions involving the distal renal artery. The greater saphenous vein is preferred by many surgeons,[6,7] except in children where arterial autografts are now the accepted reconstructive method.[8] The hypogastric artery autograft was introduced for renal replacement at our center by Edwin J. Wylie, M.D., in 1964.[8,9] The branched internal iliac artery is uniquely suited for renal replacement. It is consistently available within the same operative field in all patients affected with distal renovascular disease. It requires no donor site replacement since its absence does not produce clinically evident pelvic or gluteal ischemia. Additionally, serial follow-up evaluation of these grafts in an enlarging patient population has documented the favorable characteristics that allow it to mimic a normal renal artery, specifically, viability (growth potential), matched compliance, and durability. For all of these reasons the hypogastric artery has been our preferred conduit for renal artery replacement for over 20 years.

There no longer appears to be any advantage to autotransplantation after complex renal artery branch repair,[9,10] although this was a popular notion and is still preferred to *in situ* aortorenal bypass by Dubernard et al.[11] Their experience is uncontrolled, sequential, and highly selective, and it does not emphasize the similar improvements in aortorenal bypass that have occurred during the two decades that encompassed their report.

The results achieved in our group of selected patients with technically challenging renovascular branch lesions support our management philosophy. Clearly, there is a range of renovascular lesions that require different interventional methods. Isolated main renal artery stenosis may be satisfactorily dilated, whereas more extensive or degenerative lesions of the main renal artery are suitable for conduit aortorenal grafting (Fig. 6). Dysplastic lesions involving the primary bifurcation are ideally suited for *in situ* replacement, preferably using the branched internal iliac artery (Fig. 4). More extensive distal lesions, reoperative lesions, and selective distal renal artery disease in solitary kidneys are ideally and safely managed by *ex vivo* renal artery reconstruction using the multibranched internal iliac artery (Figs. 5 and 6). In this cohort of patients, unique characteristics that demanded a high degree of safety included bilateral disease (25%), solitary kidneys (22%), reoperative lesions (16%), pediatric age group (9%), and significant aortic disease (7%).

These techniques will restore safely normal renal arterial anatomy with native arterial autograft material, assuring life-long normal anatomy and function for the previously threatened kidney. The strategies outlined above have reliably achieved outstanding long-term total and segmental renal salvage for patients with hypertension or aneurysmal disease. The cure/improvement response in hypertensive patients exceeds 95% and will remain so indefinitely, presumably equivalent to the patient's expected life span. *Ex vivo* reconstruction is used whenever the criteria for its use are met and *in situ* techniques are impossible. *Ex vivo* reconstruction is not a compromise to *in situ* grafting but rather a complimentary extension of this technique that is achieved with only one additional technical maneuver, the reanastomosis of the renal vein.

Acknowledgments

The authors gratefully appreciate the technical assistance of Joe Mitchell and Robert Hussing with the *ex vivo* perfusions and the assistance of Shandra Metz with the collection of patient data.

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Discussion

DR. RICHARD H. DEAN (Winston-Salem, North Carolina): I rise to make three comments and ask two questions.

I congratulate Dr. Kent on an excellent presentation. The San Francisco group has one of the largest experiences in renovascular and vascular surgery in general, and we are indebted to them for presenting these data to us today.

I re-emphasize two points and stress one point not stressed in the presentation that is covered in the manuscript. The first point is the transient nature of renal dysfunction in the immediate postoperative period. We have had an experience with slightly fewer numbers. We have used *ex vivo* reconstructions in 34 patients at this point and have similarly noted a mild transient elevation in the serum creatinine levels, all of which have returned to normal by discharge. In contradistinction is the borderline patient, in whom one elects to do the *in situ* repair assuming that it can be done in an appropriate amount of time, we have noted a few patients with permanent deterioration in renal function when electing that route. I believe the point being that a more liberal use of *ex vivo* reconstructions for these patients is appropriate.

The second point is in contrast to their experience. Living in a somewhat more deprived portion of the United States than San Francisco, we have never been able to afford the Belzer pump. I would simply remind those interested members and guests that one can accomplish the same by an extremely long IV pole, a bucket of ice, and the electrolyte preservative solution hung by the same.

(Slide) I would like to stress one point that is made in their manuscript, that is, the reconstructive component of their procedure. In the initial presentations of *ex vivo* repairs, it was a technique that was married to autotransplantation. I believe the San Francisco group as well as ourselves strongly believe that this is a byproduct of the origin of these techniques from transplant surgeons. In this relatively young group in whom the replaced kidney is expected to work for five, six, or seven decades, a technique which employs a partial occlusion clamp on the vena cava, ellipse of a portion of the cava, then replacement of the kidney back in the renal fossa with reanastomosis to the tangential cavotomy, is preferable to autotransplantation to the pelvis.

I ask two questions of the authors. First, in noting that they routinely use hypogastric artery graft for all patients, I wonder if they have had any episodes of aneurysmal degeneration of their hypogastric arterial grafts. Secondly, in the patients who required bilateral procedures, I ask whether the authors would comment on whether or not they use bilateral hypogastric autografts, and if so, if they have had any late complications of this such as impotence or pelvic claudication.

DR. ROBERT C. LIM, JR. (San Francisco, California): I congratulate Dr. Stoney and his group for sharing their experience with us. I rise to emphasize that the key to his success is renal preservation.

We described a technique of *ex vivo* renal vascular surgery about 20 years ago in its selective use in trauma. Cooling the kidney with cold Ringer's heparinized saline solution was used since we do not have an elaborate perfusion pump. This remains a good technique in preserving renal function.

We, too, elect reconstruction of secondary and tertiary branches of the renal artery, then reimplanting the kidney close to its original position without disturbing the ureter.

I ask the authors one question. Do they have any thoughts or suggestions, since our technique was described 20 years ago, of improvements in preserving renal function in *ex vivo* renal surgery in a hospital where renal transplantation is not done?

DR. RONALD STONEY (Closing discussion): The comments that you just heard I believe emphasize some of the issues that we hope you would take away from this presentation, and one of them is the selective use of *ex vivo* repair in certain difficult distal lesions and *in situ* repair of more simple lesions of the primary renal bifurcation.

Dr. Dean and Dr. Lim both suggested that you might be able to achieve the same degree of renal protection using hypothermic flushing as perfusion preservation. Fred Belzer pioneered this technique in our hospital, and we, of course, have had the use of his pulsatile perfusion apparatus, which Dr. Salvatierra and I prefer, to simplify the dissection of diseased distal renal artery branches.

Hypothermic flushing will extend the ischemic tolerance of the kidney, but I believe continuous hypothermic perfusion evenly cools the entire kidney more efficiently.

The arterial autograft, in branched or straight configuration, matches the renal artery in size and branch location and thereby lends itself ideally to renal artery replacement. The ideal arterial graft requires the sacrifice of one internal iliac artery. There have been no instances of postoperative pelvic ischemia that we could detect, and we have not had occasion to remove both hypergastric arteries. If one needed a longer arterial autograft to repair renal arteries, the internal iliac and a segment of the external iliac can be harvested. The external iliac segment is thus replaced with a prosthetic graft to restore arterial continuity. It would be easier to redo a failed donor site graft repair some time later rather than redo a renal artery repair failure, which are reported following saphenous veins or prosthetic aortorenal grafts.

There have been only five males in this series of 55 patients, and impotence has not been encountered in this group, nor in other male patients 10 and nearly 20 years following hypogastric artery aortorenal grafts for main renal artery repairs that were not presented today.

The orthotopic location was emphasized by both discussants, and we agree with that method, rather than replacing the reconstructed kidney in the pelvis.

Ex vivo repair really is selective and complementary adjunct to the techniques available for main renal artery bifurcation branch repair. The method of renal preservation used depends on convenience and familiarity.

Beware of under utilizing *ex vivo* repairs for complex distal lesions as we did in a few cases. Dr. Dean correctly emphasized that slight worsening of renal function occurred only after *in situ* repairs and never after an *ex vivo* repair. We believe we can provide better renal protection particularly for kidneys that already have renal dysfunction using perfusion preservation.

The graft selected for renal artery replacement should be autogenous, and artery as well as vein are available. We believe if the goal of the reconstruction is creating a normal renal artery for the rest of the patients' life, the choice must be an arterial autograft.

3% NaCl and 7.5% NaCl/Dextran 70 in the Resuscitation of Severely Injured Patients

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Cardiovascular resuscitation of the severely injured patient in the field remains unsatisfactory because large volumes of intravenous fluid are needed to keep up with ongoing blood losses and because only small volumes of fluid can be given. In the first study reported here, small volumes (≤ 12 mL/kg) of 3% NaCl were given to patients who were having surgery for severe injuries. The 3% NaCl restored blood pressure, pH, and urine output with approximately one half of the cumulative fluid requirement of patients who received isotonic fluids ($p < 0.05$). In a second study, 7.5% NaCl/dextran 70, 250 mL, was given in a prospective, randomized, and double-blinded trial to injured patients in the field. Blood pressure in the hypertonic/hyperoncotic group increased 49 mmHg during transport ($p < 0.005$); blood pressure in patients given lactated Ringer's solution increased 19 mmHg (NS). Survival favored the hypertonic/hyperoncotic group. The 7.5% NaCl/dextran 70 solution appears particularly promising for treatment of injured patients in the field.

CONVENTIONAL ISOTONIC FLUIDS have to be given in large volumes to resuscitate the severely injured patient. This becomes a problem in pre-hospital resuscitation because the constricted veins of the patient in hypovolemic shock make percutaneous insertion of large-bore catheters difficult. As a consequence, emergency medical personnel, using the relatively small-bore cannulae available to them, cannot infuse sufficient volumes of fluid to keep up with ongoing losses.[1,2]

A combination of hypertonic NaCl and dextran 70 could solve this problem. We have found that a combination of 7.5% NaCl and 6% dextran 70 is particularly effective in resuscitating animals from hemorrhagic shock, even when the solution is given in volumes as small as 5 mL/kg, volumes small enough to infuse in the field.[3,4] Solutions of this nature improve survival in lethal hemorrhage models[5,6] and can support circulation in an arrested hemorrhage model for at least 30 minutes[3,4]: sufficient time to keep an injured patient alive during transport to the hospital.

The two trials described in this report developed out of our laboratory work. The first trial studied the effects of infusing 3% NaCl to patients who were having surgery for acute severe injuries; the second studied infusion of 7.5% NaCl/dextran 70 to injured patients in the field.

Methods

Operating Room Study

Injured patients undergoing surgery who had had at least one episode of hypotension with a systolic blood pressure of 70 mmHg or less, or who had required resuscitative solutions in volumes exceeding 6 liters, were considered for inclusion if they: (1) were 18 years of age or older; (2) had been injured no longer than 6 hours previously; (3) had received at least 2 units of blood; (4) had received at least 15 mL/kg of crystalloid solutions during the previous hour; and (5) were likely to require at least 15 mL/kg for the next hour to maintain blood pressure and urine output.

After entry into the protocol, the patients were given, over 1 hour, either 3% NaCl (1028 mOsm/kg, 4 mL/kg) or lactated Ringer's Solution (12 mL/kg), the solution administered depending on the attending surgeon. At the end of both the first and second hour, the patient's

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fluid needs were reassessed. If at least 15 mL/kg of fluid had been required over the preceding 60 minutes to maintain blood pressure and urine output, they were given another infusion of the test solution. The test solution was withheld if the patient had required less than 15 mL/kg of fluid, or if the serum sodium concentration, as reported by the hospital laboratories, came to exceed 155 mEq/L. Thus at the end of the 3-hour study period, a patient in the 3% NaCl group could have received a total of 12 mL/kg of the hypertonic solution, although most received less. In addition to the test solution, all patients in both groups were given supplemental isotonic fluids as needed to maintain blood pressure and urine output at the best possible levels during and after the study.

The research nurse was called into the hospital for each patient, and the study was started only after she was present to make the required measurements. The predetermined hypothesis for the study was that the 3% NaCl group would achieve resuscitation with less fluid, during the infusion period, than that needed with isotonic solutions.

Field Trial

Trauma victims treated by our Life-Flight nurses, under our direction, who were transported by helicopter were considered for inclusion if they: (1) were at least 18 years old; (2) had been injured within the previous 6 hours; (3) had a sinus complex on electrocardiogram; and (4) had a systolic blood pressure of 100 mmHg or less, measured by the flight nurse at the scene or at any time during transport to the hospital. Patients were excluded if they were pregnant or if they had pre-existing hepatic, renal, cardiac, or neurological disease.

Plastic bags containing 250 mL of 7.5% NaCl/4.2% dextran 70 (2400 mOsm/kg) were prepared by the hospital pharmacist by adding 75 mL of a 23.4% NaCl solution to 175 mL of 6% dextran 70 in 0.9% NaCl. The 4.2% dextran concentration was used as we had to dilute commercially available 6% dextran to obtain the desired 7.5% NaCl concentration. These bags, and other bags with an identical appearance but containing 250 mL of lactated Ringer's solution, were then coded and placed in the hospital's Life-Flight helicopter in an order determined by a table of random numbers. Patients entered into the protocol received the solution available in the helicopter, preceded by infusion from a coded syringe of 20 mL of dextran 1[7,8] or lactated Ringer's solution, depending on the bag of resuscitative solution they were to receive. All solutions were administered *via* peripheral vein over 5 minutes or less. Supplemental isotonic fluids were administered as necessary to restore hemodynamic stability. Once the patients arrived in the emergency room, standard therapy was initiated as warranted by their clinical condition. All personnel concerned with the care of the patients were kept blinded as to the treatment solution until the code was broken on April 1, 1987. In addition to routine clinical and laboratory measurements, plasma dextran levels were determined on admission to the emergency room and at 24 hours.[9] The predetermined hypothesis for this trial was that the patient who had received 7.5% NaCl/dextran 70 would achieve higher blood pressures on arrival in the emergency room than those who received isotonic resuscitation.

All data in the text, figures, and tables are presented as means ± 1 SD. Differences over time and between groups were analyzed by a repeated measures analysis of variance on logarithmically transformed data. Differences at particular times were analyzed by a two-tailed Wilcoxon's sign test for paired data and a Mann-Whitney test for unpaired data. Survival was evaluated by a Cox proportional hazards model, and a log rank statistic test was used to test the effect of treatment over control. The analysis was made both with and without censorship of the patients with severe head injuries. Revised Trauma Scores and Injury Severity Scores were calculated using standard techniques.[10-12] Both of the studies reported here were approved by the institution's Human Subjects Review Committee.

Results

Operating Room Study

Between July 1985 and April 1986, 1156 patients were admitted to the General Surgery Trauma Service, which performed operations on 579 patients. Twenty severely injured patients were entered into the study: 10 in the 3% NaCl group and 10 in the lactated Ringer's group. The patients had similar ages, sex distributions, Glasgow Coma Scores, Revised Trauma Scores, Injury Severity Scores, mechanisms of injury, and sites of injury at time of entry (Table 1).

The only substantial difference at time of entry between the treatment groups was time from injury to time of entry, that time being longer in the lactated Ringer's group (Table 1). This time did not seem to indicate undue delay, however. The amounts of blood transfused by the time of entry to the 3% NaCl and lactated Ringer's groups were 23 ± 18 *versus* 24 ± 17 mL/kg, and the hematocrits at the time of entry were comparable (25 ± 8 *versus* 23 ± 9 vol%). Blood pressures (Fig. 1), arterial pH (Fig. 2), urine outputs (Fig. 3), fluids administered (Fig. 4), and fluid balances (Fig. 5), at time of entry, were also comparable.

By virtue of the protocol, all 10 patients in the hypertonic group received 4 mL/kg of 3% NaCl during the first hour. During the second hour, six patients received

TABLE 1. *Patient Characteristics at Time of Entry into the Operating Room Study**

	3% NaCl (N = 10)	Lactated Ringer's (N = 10)
Age (years)	36 ± 13 (24–64)	36 ± 21 (19–87)
Sex (male/female)	9/1	9/1
Time from injury (hours)	2.1 ± 0.4 (1.5–3.0)†	3.5 ± 1.0 (2.0–5.0)
Systolic blood pressure (mmHg)	98 ± 41 (0–139)	105 ± 29 (70–142)
Heart rate (beats/min)	107 ± 39 (0–135)	114 ± 13 (95–136)
Ventilatory rate (breaths/min)	13 ± 2 (12–16)	11 ± 3 (8–16)
Glasgow Coma Score	14 ± 1 (11–15)	11 ± 6 (3–15)
Revised Trauma Score	11 ± 3 (4–12)	9 ± 5 (0–12)
Injury Severity Score	34 ± 10 (21–54)	33 ± 8 (21–47)
Mechanism of injury		
Penetrating	5	5
Blunt	5	5
Site of injury		
Head	1	0
Heart/lung	5	5
Liver/spleen	4	4
Gastrointestinal tract	3	4
Pelvic fractures	3	2
Long bone fractures	3	3

* Ranges in parentheses.
† $p < 0.01$ for difference between groups.

the 3% NaCl and, during the third hour, three patients received the solution. Four patients did not receive the solution during the second hour: two had serum sodium concentrations greater than 155 mEq/L, one had required less than 15 mL/kg during the first hour for hemodynamic stability, and one had died. During the third hour, only three patients received the solution: five were hemodynamically stable and had required less than 15 mL/kg of fluid during the previous hour, and one had a serum sodium concentration greater than 155 mEq/L. All 10 patients in the lactated Ringer's group received the test solution during all time periods because all required more than 15 $mL \cdot kg^{-1} \cdot h^{-1}$ during these hours, with the exception of one patient who died in the third hour.

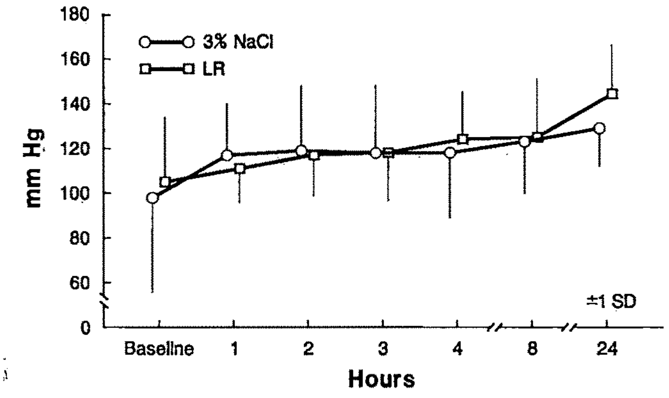

FIG. 1. Systolic blood pressure, in operating room study. Means ± 1 SD. There were no significant differences between groups.

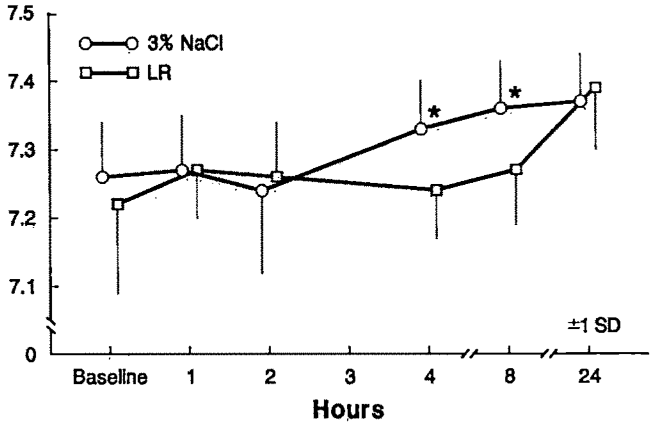

FIG. 2. Systemic arterial pH in operating room study. There were no significant differences between groups over the 24-hour period considered as a whole, by repeated measures analysis of variance, but significant differences between groups at individual time periods, by Mann-Whitney tests, as indicated by asterisks (*$p < 0.05$).

The blood pressures responded satisfactorily in both groups (Fig. 1). Arterial pH, in the face of partial pressures of CO_2 that were maintained between 38 and 42 mmHg, returned to normal sooner in the 3% NaCl group (Fig. 2). Urine outputs were greater in the hypertonic group during the time of infusion and for several hours thereafter (Fig. 3). These effects were achieved with less cumulative fluid administered in the 3% NaCl group (Fig. 4) and with smaller fluid balances (fluids infused minus urine outputs) (Fig. 5). At the end of the 24-hour resuscitation period, the 3% NaCl patients received 15 ± 12 L of crystalloid *versus* 24 ± 9 L in the lactated Ringer's group. After 24 hours, all of these differences lost their statistical significance.

Serum electrolytes, at time of entry, were comparable between the two groups and were within normal limits. Serum osmolalities, at time of entry, were slightly ele-

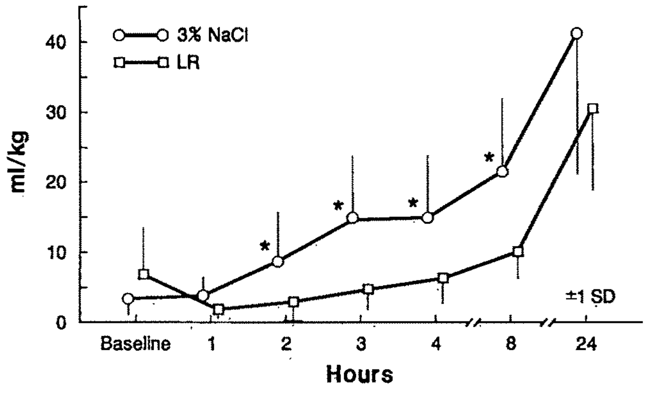

FIG. 3. Cumulative urine outputs in operating room study. There were no significant differences considering entire 24-hour period, but significant differences at individual time periods (*$p < 0.05$).

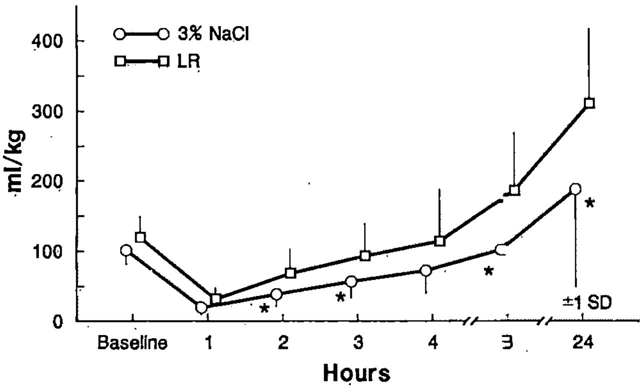

FIG. 4. Cumulative crystalloids administered in operating room study. There were no significant differences considering entire 24-hour period, but significant differences at individual time periods (*$p < 0.05$).

vated: 308 ± 20 and 303 ± 10 mOsm/kg in the 3% NaCl and lactated Ringer's groups, respectively. At 1 hour the sodium and chloride concentrations were higher in the 3% NaCl group as were the osmolalities (Table 2). These values were close to normal by 24 hours.

Modalities of treatment other than solutions administered were comparable in the two groups, including time of surgery (3.6 ± 2.1 and 5.7 ± 4.0 hours), cumulative 24-hour administered sodium (30 ± 21 and 41 ± 16 mEq/kg), and 24-hour administered blood (55 ± 91 and 60 ± 35 mL/kg). Hematocrit values at 24 hours were (28 ± 5 and 33 ± 4 vol%).

With the exception of pulmonary dysfunction, morbidity and mortality were comparable between the groups. No irritation was noted in any of the veins that were used for the 3% NaCl infusions. Seven of the patients in the 3% NaCl group and all of the patients in the lactated Ringer's group had failure of at least one organ develop after injury. Overall survival rates in the two groups were 60% in the 3% NaCl patients and 70% in the control patients.

TABLE 2. *One Hour Laboratory Data for Operating Room Study**

	3% NaCl	Lactated Ringer's
Serum sodium (mEq/L)	152 ± 6 (146–157)†	146 ± 2 (144–150)
Serum potassium (mEq/L)	3.8 ± 0.9 (2.7–5.3)	4.2 ± 0.4 (3.6–4.5)
Serum chloride (mEq/L)	117 ± 6 (112–130)†	110 ± 5 (99–116)
Osmolality (mOsm/kg)	319 ± 24 (290–370)†	313 ± 11 (289–305)
pH	7.27 ± 0.08 (7.15–7.37)	7.27 ± 0.08 (7.12–7.39)
Hematocrit (vol%)	29 ± 5 (22–40)	32 ± 4 (18–42)

* Ranges in parentheses.
† $p < 0.05$.

With respect to pulmonary dysfunction, the partial pressures of oxygen in systemic arterial blood divided by the fractional concentrations of oxygen in inspired air (P_aO_2/F_iO_2 indices) were lower in the 3% NaCl group at time of entry (240 ± 131 mmHg) but held constant for the first 24 hours, when they were 256 ± 108 mmHg (Fig. 6). The P_aO_2/F_iO_2 indices were higher in the lactated Ringer's group (380 ± 135) and gradually worsened to 197 ± 94 (Fig. 6). The days of mechanical ventilation were 14 ± 20 in the 3% NaCl group *versus* 29 ± 26 in the lactated Ringer's group. Days in the intensive care unit were 18 ± 27 and 38 ± 30, respectively. Total days in the hospital were 28 ± 36 and 68 ± 56, respectively.

Field Trial

Between May 1986 and March 1987, 355 trauma patients were transported by the Life-Flight helicopter service to the University of California Davis Medical

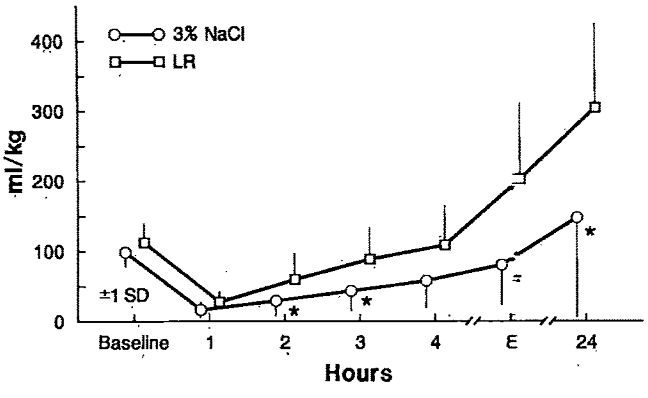

FIG. 5. Cumulative fluid balances in operating room study. There were no significant differences considering entire 24-hour period, but significant differences at individual time periods (*$p < 0.05$).

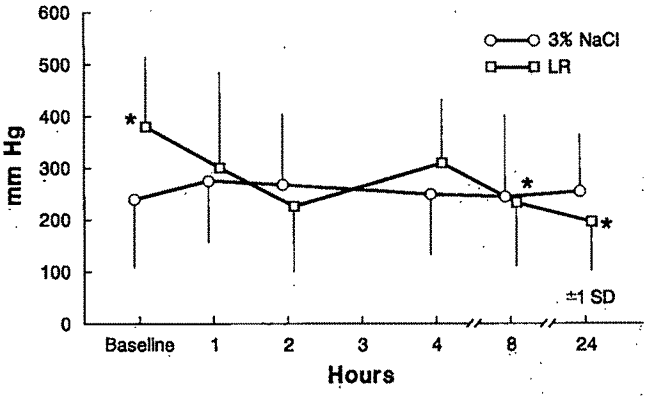

FIG. 6. P_aO_2/F_iO_2 indices in operating room study. There was a significant decrease at 8 and 24 hours in the lactated Ringer's group when compared with baseline levels (*$p < 0.05$). There was no significant decrease in indices in 3% NaCl group.

TABLE 3. *Patient Characteristics at Time of Entry into the Field Trial**

	7.5% NaCl/ Dextran 70 (N = 10)	Lactated Ringer's (N = 10)
Age (years)	25 ± 7 (19–37)	39 ± 17 (17–67)
Sex (male/female)	6/4	5/5
Time from injury (hours)	1.0 ± 0.5 (0.2–1.9)	1.3 ± 1.0 (0.3–3.3)
Systolic blood pressure (mmHg)	72 ± 29 (0–98)	69 ± 27 (0–96)
Heart rate (beats/min)	94 ± 30 (52–150)	103 ± 27 (60–150)
Ventilatory rate (breaths/min)	25 ± 6 (18–36)	27 ± 6 (24–36)
Glasgow Coma Score	10 ± 5 (3–15)	7 ± 5 (3–15)
Revised Trauma Score	9 ± 3 (4–12)†	5 ± 4 (0–10)
Injury Severity Score	26 ± 15 (9–50)	37 ± 22 (13–75)
Mechanism of injury		
Penetrating	2	1
Blunt	8	9
Site of injury		
Head	4	7
Heart/lung	5	8
Liver/spleen	4	3
Gastrointestinal tract	1	1
Pelvic fractures	3	0
Long bone fractures	3	2

* Ranges in parentheses.
† $p < 0.05$.

Center. Twenty patients were entered into the study: 10 in the 7.5% NaCl/dextran 70 group and 10 in the lactated Ringer's group. Twenty-seven patients who otherwise met the criteria for entry were excluded either because of lack of venous access or other logistical problems. With the exception of incidence of severe head injuries and perhaps age, the two groups were comparable with similar sex distributions, times from injury to entry, vital signs, mechanisms of injury, and sites of injury (Table 3). With respect to neurologic status, the patients in the 7.5% NaCl/dextran 70 group had fewer serious head injuries with resulting higher Glasgow Coma Scores, higher Revised Trauma Scores, and lower Injury Severity Scores (Table 3).

The average flight times were 13 ± 8 and 18 ± 10 minutes. Nine patients in the 7.5% NaCl/dextran 70 group received the full 250 mL. One patient, with accidental disruption of his intravenous catheter, received only 125 mL. The test solution was the only fluid administered to four patients in the hypertonic group. All patients in the lactated Ringer's group received the full 250 mL of test solution. In two patients, this was the only resuscitative fluid. Figure 7 illustrates the total volumes of crystalloid administered in flight, normalizing the data for flight time. Total fluid administered during flight, without normalization for time, was 700 ± 500 mL in the 7.5% NaCl/dextran 70 group *versus* 1300 ± 900 mL in the lactated Ringer's group. The patients in the 7.5% NaCl/dextran 70 group responded with a substantial (49 mmHg) and significant ($p < 0.005$) increase in systolic blood pressure during the flight, increasing from 72 ± 29 to 121 ± 15 mmHg (Fig. 8). Blood pressures in the lactated Ringer's group increased 19 mmHg, increasing from 69 ± 27 to 88 ± 60 mmHg ($p > 0.05$, Fig. 8). Heart rates in the 7.5% NaCl/dextran 70 group increased from 94 ± 30 to 116 ± 21 ($p < 0.01$, Fig. 9); heart rates in the lactated Ringer's group remained the same (97 ± 41 and 103 ± 23). Ventilatory rates increased slightly: 24 ± 4 to 29 ± 6 ($p < 0.05$) in the 7.5% NaCl/dextran 70 group and 27 ± 6 to 30 ± 5 in the lactated Ringer's group. There was little change in the Glasgow Coma Scores: 10 ± 5 to 11 ± 5 in the 7.5% NaCl/dextran 70 group and 7 ± 5 to 7 ± 5 in the lactated Ringer's group. None of the patients in either group died during transport.

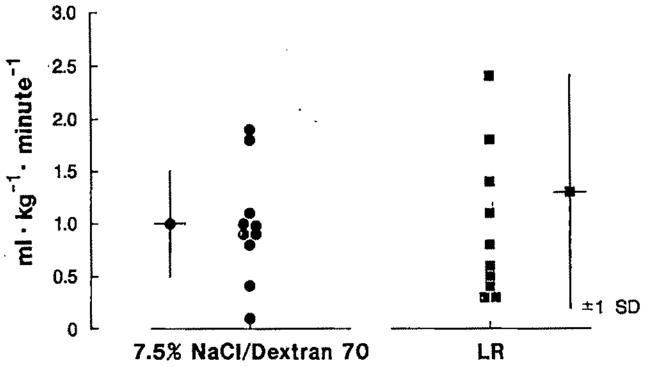

FIG. 7. Fluid administered during helicopter flight in field trial, as $mL \cdot kg^{-1} \cdot min^{-1}$ to compensate for flight time. Individual patients with means ± 1 SD.

The serum sodium concentrations, chloride concentrations, and osmolalities were significantly elevated by time of admission to the emergency room in the 7.5%

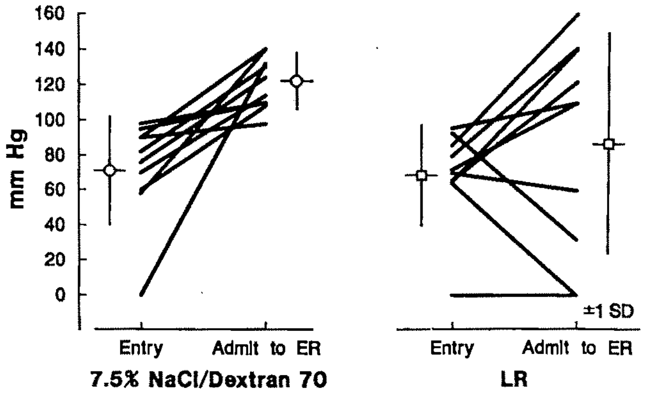

FIG. 8. Systolic blood pressures in field trial. There was a significant increase ($p < 0.005$) in patients given 7.5% NaCl/dextran 70.

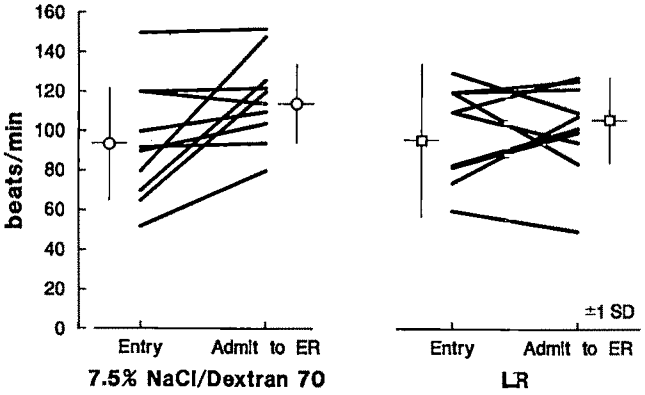

FIG. 9. Pulse rates in field trial. There was a significant increase ($p < 0.01$) in patients given 7.5% NaCl/dextran 70.

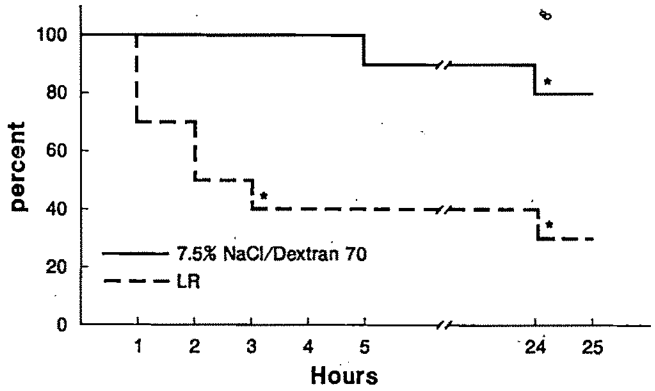

FIG. 10. Survival in field trial. Asterisks represent patients with severe head injuries who were allowed to die at the times indicated. All patients who survived the first 24 hours are still alive.

NaCl/dextran 70 patients (Table 4). These abnormalities were well resolved within several hours. The serum potassium levels were less than 3.5 mEq/L in three patients in the 7.5% NaCl/dextran 70 group, the lowest being 2.9 mEq/L. No ventricular dysrhythmias developed with the hypokalemia. Plasma dextran levels in the 7.5% NaCl/dextran 70 group, on admission to the emergency room, were 3.0 ± 0.7 mg/mL (N = 10); by 24 hours they had fallen to 0.9 ± 0.4 (N = 8). No preinfusion laboratory values are available.

Two alert patients in the 7.5% NaCl/dextran 70 group remarked on a sensation of warmth in their extremities during the infusion, and the nurses reported marked flushing in four patients who received the hypertonic solution. These symptoms were transient. No phlebitis developed in any veins used for the infusions. There were no type or cross-matching problems.

Survival of the patients in the two groups is shown in Figure 10. One patient in the 7.5% NaCl/dextran 70 group died at 5 hours with disseminated intravascular coagulation; the second patient was allowed to die at 24 hours with a severe head injury. One patient in the lactated Ringer's group, with no blood pressure in the field and none in the emergency room, died in the operating room at 1 hour with a shotgun wound to the abdominal aorta and inferior vena cava. One patient died at 1 hour in the operating room with a ruptured left ventricle; and one patient died at 1 hour from a severe head injury. One patient in the lactated Ringer's group died at 2 hours with a severe head injury; a second patient died at 2 hours with disseminated intravascular coagulation. The remaining two deaths in the lactated Ringer's groups, at 3 and 24 hours, were in patients who were allowed to die with severe head injuries. Overall survival was better ($p < 0.05$) in the 7.5% NaCl/dextran 70 group, even when censoring the patients with severe head injuries.

TABLE 4. *Laboratory Data for Patients in Field Trial at Time of Arrival in the Emergency Room**

	7.5% NaCl/Dextran 70	Lactated Ringer's
Serum sodium (mEq/L)	153 ± 4 (144–159)†	142 ± 5 (32–150)
Serum potassium (mEq/L)	3.6 ± 4 (2.9–4.4)	3.9 ± 0.3 (3.5–4.3)
Serum chloride (mEq/L)	119 ± 5 (106–127)	109 ± 6 (98–117)
Osmolaltiy (mOsm/kg)	337 ± 23 (313–358)	315 ± 28 (279–345)
pH	7.27 ± 0.09 (7.10–7.40)	7.34 ± 0.30 (7.06–8.04)
Hematocrit (vol%)	28 ± 7 (16–38)	31 ± 8 (20–41)

* Ranges in parentheses.
† $p < 0.01$.

Discussion

This is not the first report of using hypertonic sodium chloride solutions in humans. In the 1920s, Silbert,[13] working at Mt. Sinai Hospital in New York City, used peripheral intravenous infusions of 5% NaCl to treat patients with Buerger's disease. Injections in volumes as large as 300 mL, given over periods as short as 10 minutes, produced flushing and warmth in both ischemic and nonischemic parts of the body but produced no instances of phlebitis and no neurologic abnormalities. Later on, hypertonic sodium-containing solutions were used for correction of electrolyte abnormalities and, by the 1970s, moderately hypertonic solutions were being used to resuscitate patients with severe burns.[14] In 1980, deFelippe et al. reported that a 7.5% NaCl solution, in a volume of 4 mL/kg, was effective in resuscitating patients in hypovolemic shock.[15] In 1983, Shackford et al., in a well-controlled study, reported on the use of a 1.5% sodium-containing solution to maintain cardiovascular stability in patients who had elective vascular surgery.[16]

We used a 7.5% NaCl/dextran 70 solution in the helicopter study because combinations of hypertonic sodium salts with dextran 70 are the most effective fluids that we have found for resuscitation of animals from shock. Such a solution, when given to animals in shock, dramatically restores blood pressure and cardiac output within 2 minutes of infusion.[3,4] It also restores acid-base balance, urine output, and oxygen consumption.[4] A 7.5% NaCl/6% dextran 70 solution has a calculated osmolality of 2400 mOsm/kg, the dextran adding only 1 mOsm/kg to the tonicity.[17] Its oncotic pressure, generated solely by the dextran, is about 75 mmHg, a high value created by the properties of the long chain polysaccharides moieties and a value substantially greater than that expected based on their concentrations and molecular weights.[17] The immediate beneficial effects of these hypertonic/hyperoncotic solutions arise from the hyperosmolality *per se* and are generated by plasma volume expansion,[3,4,18-20] enhancement of myocardial contractility,[21-25] and augmentation of organ blood flow mediated by dilation of precapillary resistance vessels.[21,26-30] These hyperosmolar-induced benefits dissipate within 15 minutes, however, as plasma volume reverts to shock levels.[3] The addition of dextran 70 to the 7.5% NaCl prevents this deterioration,[3] and the beneficial effects of the hypertonic/hyperoncotic combination can easily last for 30 minutes,[4] at least in arrested hemorrhage models. This would be enough time to transport most patients to the hospital.

The results of the operating room and helicopter trial are consistent with and support the conclusions reached in the animal work and suggest that a hypertonic NaCl/hyperoncotic dextran combination may be beneficial in the field treatment of severely injured patients. The 3% NaCl solution produced excellent resuscitation of severely injured patients with good restoration of blood pressure, acid-base balance, and urine output, and achieved these beneficial effects with less fluid during the resuscitative phase than that required with conventional isotonic fluids. The 7.5% NaCl/dextran solution was safe in the prehospital setting and produced substantially higher blood pressures than those produced by conventional treatment despite the control patients being given substantial amounts of isotonic fluid. The 7.5% NaCl/dextran 70 solutions also appeared promising with regard to improving survival (Fig. 10).

Administration of a solution of this sort to patients does pose certain theoretical risks, however. The dextran could cause bleeding abnormalities and could interfere with cross-matching of blood. The hypertonicity of the solutions could cause phlebitis. Rapid increases in osmolalities and in serum sodium and chloride concentrations could induce neurologic abnormalities,[31-33] and rapid expansion of the extracellular space could produce hypokalemia[4,34] and arrhythmias. Lastly, rapid restoration of blood pressure and perfusion could lead to resumption of bleeding from severed vessels that had gone into spasm or that had clotted with the initial shock insult.

None of these theoretical risks[35-38] was realized in any of the patients, as best we could determine. The amount of dextran administered was small and resulted in low plasma dextran concentrations. No unexplained clotting abnormalities developed in any of the patients,[35,38] and the blood bank had no difficulty in cross-matching blood.[36,37] Hypertonicity by itself does not necessarily induce phlebitis if infusion times are limited. Radiographic contrast media have osmolalities approaching that of the 7.5% NaCl/dextran 70 solution, as does the sodium bicarbonate (1800 mOsm/kg) that is used in resuscitation of patients from cardiac arrests. The 7.5% NaCl/dextran solution does not cause phlebitis in animals,[39] and we found none in our patients. It would seem important, however, to avoid extravasation.

Osmolalities and serum sodium and chloride concentrations increase rapidly with infusion of these solutions, but this should not necessarily be a problem. Rapid increases in osmolality can damage the central nervous system, but, to our knowledge, this has only occurred in patients who have had very low serum sodium concentrations (less than 115 mEq/L) before the onset of hyperosmolality or in patients with established liver disease.[33] None of our patients had chronic hepatic or cardiac disease (and it would seem wise not to use these hypertonic solutions in patients with obvious signs of cirrhosis or congestive heart failure). We noted no central nervous system abnormalities that could have been attributed to the infusions. The Glasgow Coma Score even improved slightly, but insignificantly, in the patients given the hypertonic solutions, consistent with the finding that hypertonic sodium-containing solutions reduce intracranial pressures in animals resuscitated from shock.[40-42]

Some of our patients became modestly hypokalemic with the infusions, probably because the resuscitative fluid is potassium free and because it rapidly expands the extracellular space.[4,34] The solution did not cause any arrhythmias, and rapid expansion of plasma volume is probably worth the risk of hypokalemia in patients with major hemorrhage. Nonetheless, it currently would seem best to use these solutions with care in patients who might be taking digitalis compounds. The risk of rebleeding with re-establishment of blood pressure did not seem to be a problem in these studies.

In summary, small volumes (≤ 12 mL/kg) of 3% NaCl, when given to patients who have surgery for severe injuries, restored blood pressure, pH, and urine output with approximately one half of the cumulative fluid requirement of patients who received isotonic fluids. In a field trial, administration of 7.5% NaCl/4.2% dextran 70, in even smaller volumes (250 mL), resulted in augmented blood pressures during helicopter transport and tended to improve survival when compared with the lactated Ringer's group. This solution appears promising for the field resuscitation of injured patients.

Acknowledgments

We thank the Life-Flight nurses, Colleen Perry, B.A., and Dr. Wayne Gannaway of Pharmacy Services at the University of California, Davis, Medical Center, Sacramento.

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Discussion

DR. GEORGE F. SHELDON (Chapel Hill, North Carolina): This is a useful study as it addresses both the conceptual and logistic problems of prehospitalization resuscitation. Most studies of prehospital resuscitation show that in severely injured patients it takes about 10 minutes to initiate intravenous therapy. Initiation of intravenous therapy before arrival at the hospital results in less than 1 liter of fluid actually being administered.

It is of interest that in this study 1300 mL of the Ringer's lactate control were administered, which puts it well outside of the usual amount that most patients receive during pre-hospital resuscitation. A solution that will maintain hemodynamic integrity with low volume is of potential use. The authors are to be congratulated for a well-designed, difficult study.

I have several questions. Dr. Holcroft alluded to the fact that there appeared to be some direct effect on the myocardium from the solution. Some years ago, Dr. Samuel Powers, just before his death, was using dextran and observing effects in shock resuscitation of dextran directly on the myocardium. I believe most of that work was not completed. I wonder if Dr. Holcroft could speculate on the mechanism of dextran effect on the heart?

I am surprised the earlier studies showed membrane potential returning to normal with hypertonic resuscitation fluid because one would postulate that fluid would be drawn from the cell. Perhaps Dr. Holcroft could give us an explanation.

Finally, what is the limit of the amount of fluid that can be safely administered? As Dr. Clowes suggested, when a new fluid resuscitation routine comes along, great potential for misuse exists. I hope that the usefulness demonstrated in this study is not subverted into inappropriate use; perhaps the most obvious inappropriate use that might occur would be giving volumes that were excessively hyperosmolar in inappropriate amounts.

I believe this is an important study that addresses a significant problem.

DR. DONALD TRUNKEY (Portland, Oregon): I was intrigued by this study and had the opportunity to review the manuscript. Dr. Holcroft has shown that hypertonic saline and dextran combination has a major advantage in the prehospital setting and more probably in the combat situation, where small volumes could do what larger volumes in the past have been required to do.

The thing that is unique about this study is that he has shown that this combination of drugs or resuscitation fluids has a very positive contribution to increased flow. Specifically, he showed in his animal study and then in his flight study that there is a decrease in systemic vascular resistance that is probably due to the hypertonic saline. He showed a tendency toward an increase in heart rate, and both of these mechanisms could clearly increase flow.

He has not addressed in his paper stroke volume, although one would presume that would be increased with the increase in volume or plasma refill, but it was not specifically measured.

The questions that come out of this study are multiple but I would like to confine my questions to three or four.

In his manuscript Dr. Holcroft shows the PO_2/FIO_2 ratio was higher in the Ringer's lactate group, but then it dropped.

The question is: was central venous pressure kept within normal ranges? I cannot explain why the P_aO_2/FiO_2 ratio was initially better in the Ringer's lactate group than the hypertonic saline group and then fell significantly lower.

What happened to pulmonary vascular resistance? Did it fall as did systemic vascular resistance? Was there an effect on the microemboli insult to the lungs? If you did measure pulmonary vascular resistance then what role does dextran have? Is it acting as a rheologic agent in the pulmonary vasculature? Is it acting as a free radical scavenger?

Finally, did you measure extravascular lung water in these patients once they were resuscitated?

My only concern is that you did show a statistical significance in regards to the survivability in the hypertonic saline group. Do you have a type 2 error because of the small numbers?

DR. JAMES D. HARDY (Jackson, Mississippi): (Slide) I rise to offer additional support to the results and conclusions presented in this excellent report.

Some years ago, we infused in 17 patients 1 L of 3% sodium chloride over 1 hour (Surg Forum 1955; 5:465). Total body water was measured with heavy water, extracellular fluid was measured with sodium thiocyanate, and plasma volume was measured with Evans blue dye.

It may be seen that the 3% sodium chloride reduced intracellular fluid from the average of 21 L to 16 L. Of course, this reduction is based on the thiocyanate space measurement. Extracellular fluid increased from 15 L to 20 L, and plasma volume increased from 3 L to 4 L.

To be certain, this methodology has been improved over the past 30 years, but the sizes of these changes indicate that 3% sodium chloride does, in fact, change these spaces.

DR. PAUL R. SCHLOERB (Rochester, New York): Dr. Holcroft has provided convincing evidence of the superiority of hypertonic saline over isotonic lactated Ringer's. My question is: why didn't you use hypertonic lactated Ringer's solution?

DR. FRANCIS D. MOORE (Boston, Massachusetts): I thank Dr. Blaisdell and Dr. Holcroft for this paper and for allowing me to look over the manuscript.

During World War II, Taber and Rosenthal, working for the Office of Scientific Research and Development (which later became the NIH extramural grants program), did a study in burned rats and mice showing that hypertonic saline would produce rapid resuscitation.

This was not taken up clinically and was not used often. Periodically since then about once every 10 years, there has been a flurry of interest in this topic and the rediscovery of the hypertensive effects of hypertonicity.

I congratulate Dr. Holcroft and Dr. Blaisdell for their work. I also congratulate and in a sense commiserate with the physiologic mechanisms of the human body that has learned to tolerate an injection intravenously of sea water, which has been known for thousands of years to be lethal if taken internally.

Sea water is about 3% sodium chloride, a sodium concentration of about 600 mEq/L, about four times that of isotonic solution. Here, our surgical colleagues were up to higher than that in their prescription for intravenous salt.

The body can only do two things when faced with such a potentially lethal hypertonic load: excrete and dilute. Do not forget that progressive hypertonicity is always fatal when the sodium goes over about 175–180 mEq/L. This has been a mechanism of death in everything from newborn nurseries to castaways in the ocean or in the desert.

The water for this dilution comes in part from cell water as they believed, and as Dr. Hardy's study nicely demonstrates, but not entirely. This new water also arises by sucking water out of transcellular spaces in other parts of the body (joints, gut, brain) into the PV and ECF. However, there is a limit and you cannot go on doing that forever. Therefore, you must provide new water in moderation to float out the salt without overhydrating the patient.

As to excretion, their manuscript shows that their patients' kidneys were working overtime to keep up with this tremendous load of salt by excreting urine (probably hypertonic) in large quantities. I would be interested to know what the composition of that urine is.

So the body can "take it." If the load is not too serious, it will live through it! And, the body gets a blood pressure boost. I agree that hypertonic sodium salts have a pharmacologic effect. Do not ever underestimate the pressor effect of the sodium ion.

My main concern about this paper is the concept that this sort of treatment should be used "in the field." In what field? In a battlefield, the wounded (lying often in the jungle or the desert) are terribly thirsty. They are always missing water. They crave water, spring water, clear water, sodium-free water. If this highly concentrated salt solution is given to larger numbers of military casualties who cannot get to water they are going to get severely hypertonic and die in hallucinations with high fever and plasma sodium concentration over 175 mEq/L. They can be restored to normal by giving some free water or some water with a low amount of sodium.

This method is interesting. It has been tried before. It is a pressure boost. These workers have done a good job of showing us what a boost it gives. However, to give this dangerous challenge to large numbers of wounded people who do not have any access to the water that will let their bodies handle this intravenous load of sea water could be potentially lethal. We should be very cautious about recommending it too widely.

DR. WILLIAM STAHL (Bronx, New York): I congratulate Dr. Holcroft. We did the same study in dogs using a more severe model. We have mostly penetrating injury in our trauma center. Humans bottom out in 10 minutes; therefore, we bottomed the dogs out in 15 minutes and randomly assigned them to Ringer's solution, hydroxyethyl starch, or a mixture of hydroxyethl starch and 3% salt.

These animals were kept bleeding 15 minutes "on the street," 15 minutes "in the bus," 15 minutes "in the emergency department," before we stopped the bleeding. There is no question that the mixture of colloid and hypertonic salt restores cardiac index as well as blood pressure and produces better perfusion. I believe that with a little safer concentration of salt, 3% *versus* 7.5%, and the addition of some colloid, you can optimize the method for expanding volume.

In these animals we gave the amount equivalent to what you would give during ambulance transportation. That is 1 L to 1200 mL for an average adult, with no untoward effect. I agree that too much hypertonic salt might be a problem. We discontinued the hypertonic solution as soon as the animals theoretically reached the emergency department. However, I believe for the short term, limited volume, resuscitation, the combination of 3% salt, and colloid is a better solution.

DR. G. TOM SHIRES (New York, New York): May I just say Dr. Moore and I have not always agreed initially, but we have usually agreed ultimately. This time, without any data, I agree with him initially and totally. Like Dr. Moore, we have seen a lot of things, hypertonic and extraneous, come and go: everything from oxypoly gelatin to polyvinylpyrrolidone to hypertonic solutions, and as Dr. Moore said, they seem to cycle about once a decade and then they fade into oblivion. Maybe this one will be different. I do not have any data, and I do not believe Dr. Moore was quoting any, other than what we know from evolution, and I happen to agree with him wholeheartedly.

DR. GEORGE H. A. CLOWES, JR. (Boston, Massachusetts): Dr. Holcroft, I ask you briefly whether you have any evidence as to whether the beta-adrenergic activity is actually increased under these circumstances to account for the tachycardia?

DR. JAMES W. HOLCROFT (Closing discussion): Dr. Sheldon and Dr. Clowes, we do not know what the effects are on the heart yet. We believe they are mediated by beta-adrenergic receptors, but other than that, we cannot say. If the solution is given to rats that have been subjected to severe hemorrhagic shock, the solution completely restores deteriorated membrane potentials. Furthermore, it mobilizes shock-sequestered intracellular sodium and chloride. That is, animals given this hypertonic solution actually end up with less sodium and chloride inside their cells than animals given equivalent amounts of salt in an isotonic solution. How often can the fluid be given? In sheep we have given it on multiple occasions. The best response is with the first administration. After that, the solution does not work as well.

Dr. Trunkey, we do not have measurements of cardiac indices, extravascular lung waters, pulmonary vascular resistances, or any of the other hemodynamic measurements that we would like to have in these patients. The patients in both studies could not be monitored thoroughly. The role of dextran in the animals is very convincing. If you give pure 7.5% sodium chloride to sheep, you will get an excellent transient response, but that response dissipates within 15 minutes. Adding dextran allows those beneficial effects to last for at least 30 minutes.

Dr. Hardy, thank you. There is nothing new under the sun. In fact, Dr. Silbert, working in Dr. Berger's hospital in New York City in 1926, published his experience with infusion of 5% sodium chloride, using much the same total sodium dose that we currently are proposing to use in the field management of severely injured patients.

Dr. Schloerb, we have tried hypertonic acetate in combination with hypertonic sodium chloride in the sheep. The results favor the hypertonic sodium chloride slightly. Because of those early sheep experiments, we have continued to work with the sodium chloride rather than adding lactate or acetate.

Dr. Moore, we believe that the solution works, in part, by drawing water out of the lumen of the gastrointestinal tract. Many of these patients had been drinking before their accident. We believe that this is one reason why the solution worked so well. We agree that the solution should not be used in dehydrated individuals.

Dr. Stahl, I appreciate your comments. These patients not only are in shock when you pick them up, but they continue to bleed. The patients that are most likely to benefit from the solution are those who are the worst off to begin with.

Recognition and Treatment of Patients with Hereditary Nonpolyposis Colon Cancer (Lynch Syndromes I and II)

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Primary genetic factors are etiologic in at least 5–10% of patients with colon cancer. The polyposis syndromes (FPC) are easily identified examples because of the spectacular number of polyps. The hereditary nonpolyposis syndromes (HNPCC), although five times more common than FPC, are usually not recognized because they do not have such a distinctive clinical, premonitory genetic marker. Colorectal cancer expression was surveyed in 10 extended, thoroughly documented HNPCC kindreds. One hundred sixteen patients were found to have 183 colorectal cancers. Despite the striking family history, less than 5% were correctly treated by subtotal colectomy. This provided a unique opportunity to study the natural history. Five findings differed significantly ($p < 0.05$) from patients with sporadic colon cancer: (1) mean age of initial colon cancer diagnosed was 45.6 years; (2) 69.1% of first colon cancers were located proximal to the splenic flexure of the colon; (3) 18.1% had synchronous colon cancer; (4) 24.2% had metachronous colon cancer develop with life table analysis showing the risk for a metachronous lesion at 10 years to be 40%; and (5) only 23.3% of cancers were located in the sigmoid colon or rectum. Based on this data, it is recommended that the family history of all patients with a newly diagnosed colon cancer be evaluated for evidence of this syndrome. If an autosomal dominant inheritance pattern emerges, an in-depth genetic investigation is indicated. When HNPCC is confirmed, the following recommendations apply: a subtotal abdominal colectomy is indicated at the time of the initial colon cancer because of the risk of synchronous and metachronous lesions. The rectum should be spared in favor of careful lifetime surveillance because of the proclivity for proximal colon cancer involvement. As yet unaffected members of a newly diagnosed HNPCC kindred who are in the "direct genetic line" should be cautioned that they are at 50% risk and must begin an intensive surveillance program beginning in the third decade with careful attention to the right colon. Patients from newly diagnosed HNPCC families who have had a previous conventional colectomy for colon cancer should, at the very least, enter an intensive surveillance program; a prophylactic completion subtotal colectomy should be considered for patients who are less than totally compliant.

From the Departments of Surgery, Medicine, Pathology, and the Hereditary Cancer Consultation Center, Creighton University School of Medicine, Omaha, Nebraska

IT IS ESTIMATED that colorectal cancer will develop in 145,000 patients in the United States in 1987. Sixty thousand individuals will die of the disease.[1] Five to ten per cent of these malignancies are now recognized as being hereditary.[2] A fraction of these patients from this hereditary subset are members of families with familial polyposis coli (FPC) or a related syndrome and are thereby easily recognized because of the distinctive clinical marker of multiple adenomatous polyps. Unfortunately, hereditary *nonpolyposis* colon cancer (HNPCC), which is more than five times as common as FPC, does not have such a distinctive clinical marker.[3] Thus, a patient with a newly diagnosed colon cancer who is a member of an HNPCC kindred may not be recognized as such and is inappropriately treated with a conventional colectomy as one would recommend for sporadic colon cancer.

The purpose of this paper is to make recommendations concerning first, the recognition of patients with HNPCC by simple analysis of the family history and second, management strategy that is distinctly different from FPC or sporadic colon cancer. These recommendations are based on an in-depth analysis of 10 HNPCC kindreds to determine the natural history of the condition.

Methods and Materials

The study population consists of 10 kindreds followed at the Creighton University Hereditary Cancer Institute. The index patient was referred by either a physician or a

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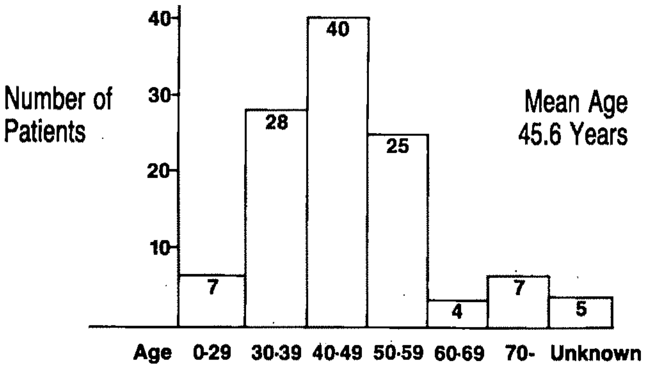

FIG. 1. Age distribution at the time of initial colon cancer diagnosis.

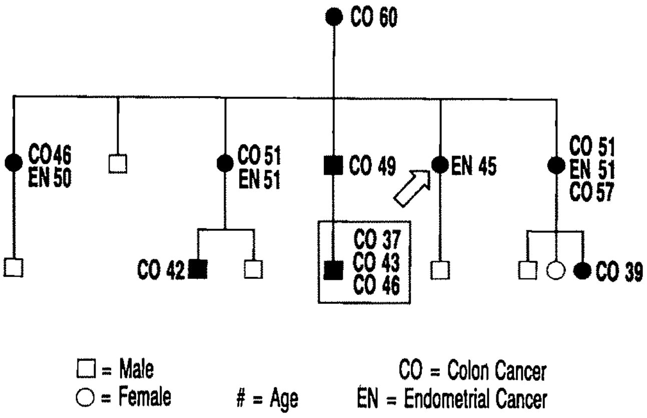

FIG. 3. A partial family pedigree of one of the HNPCC kindreds in this study. The patients highlighted by the box and the arrow are discussed in the text.

member of the family because of a perception of an inordinately high incidence of cancer. The patients with colon cancer in these families were uniquely suited for study of the natural history of HNPCC because less than 5% were treated appropriately by subtotal colectomy at the time of initial diagnosis. Extensive pedigree analysis through multiple generations disclosed that these 10 families fulfilled previously defined criteria of HNPCC.[4] Verification of family reports of cancer was accomplished whenever possible by primary medical document review including medical records, operative notes, pathological reports, and autopsy and death records.

Statistical Methods

Descriptive statistical methods were used in the analysis of these data. Categorical variables were described with frequency distributions and proportions; continuous variables (*i.e.*, age) were described additionally in terms of means and standard deviations. Inferences about differences from the unselected population of colon cancer cases were made by establishing 95% confidence intervals and comparing these with the closest comparable values found in the general population literature.[1,5-7] The incidence of metachronous colorectal cancer was also described using life table analysis, taking the initial colorectal diagnosis as the start of observation and calculating risk over a specified interval as cumulative proportion surviving through that interval subtracted from one.

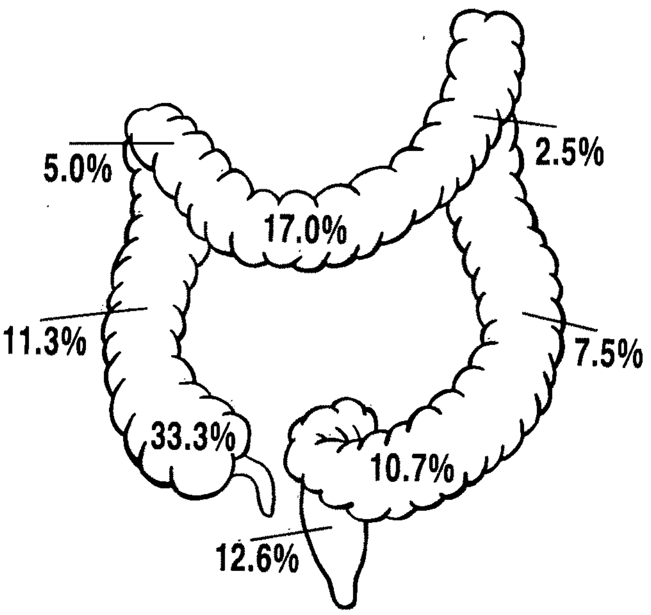

FIG. 2. Location of the first colon cancer in 113 patients. Three patients are not included because the site could not be unequivocally documented.

Results

One hundred sixteen individuals were identified with 183 histologically confirmed colorectal cancers. There were 52 females and 64 males. Mean age of colon cancer onset was 45.6 years. The age distribution is depicted in Figure 1. The location of the first colon cancer was unequivocally documented in 113 of the 116 patients. The distribution is shown in Figure 2; 69.1% were located proximal to the splenic flexure and only 23.3% involved the sigmoid colon or rectum. Synchronous colon cancer was defined as any additional colon cancer occurring within 1 year of another. Thirty-three colon cancers in 21 patients fit this description for a synchronous colon cancer rate of 18.1%. If a colon cancer was diagnosed more than 1 year after a preceding colon malignancy, it was considered metachronous. This was found in 34 colon cancers in 28 patients for a metachronous colon cancer rate of 24.2%. Life table analysis disclosed the cumulative incidence of metachronous colon cancer to be 40% by 10 years. Colon cancer incidence was consistent with an autosomal dominant inheritance pattern in all 10 families, and representative pedigrees are depicted in Figures 3 and 4. Extracolonic cancers were found in

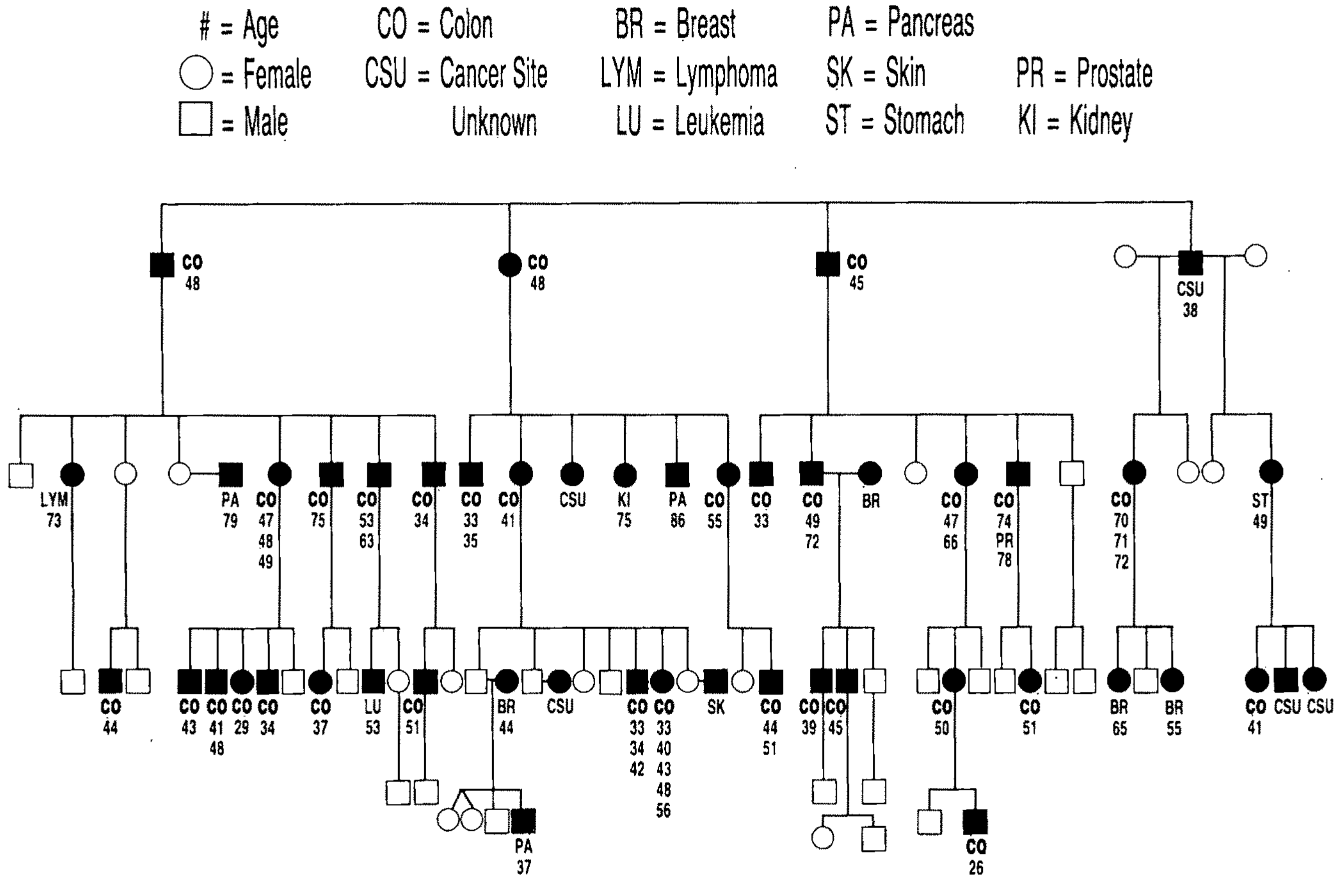

FIG. 4. A partial family pedigree of another family in this study. The multiple operative procedures necessitated by the synchronous and metachronous colon cancers could have been avoided if the presence of the syndrome was appreciated at the initial diagnosis.

151 members of the 10 families with an unusually high incidence of female genital tract lesions, *e.g.*, 32 endometrial cancers. Table 1 reflects the distribution of all cancers. The findings of early age of onset, proximal colon involvement, relative sparing of the sigmoid colon and rectum, and the high incidence of synchronous and metachronous colon lesions differed significantly at the $p < 0.05$ level when compared with representative published reports dealing with sporadic colon cancer[5–7] (see Table 2).

TABLE 1. *Comparison of Distribution of Cancers with the General Population*

Site (No.)	HNPCC Patients (%)	1987 Estimate for General Population[1] (%)
Colon and rectum (183)	55	15
Female genital tract (45)	14	7
Skin (19)	6	3
Lymphoma, leukemia (9)	3	5
Breast (17)	5	14
Stomach (13)	4	2
Urinary tract (17)	5	18
Pancreas (4)	1	3
Lung (1)*		15
Miscellaneous (11)	3	18
Cancer site unknown (15)	4	
Total (334)	100	100

* The curiously low incidence is currently under investigation.

Discussion

HNPCC is a syndrome that affects a significant percentage of the total colon cancer population but is not

TABLE 2. *Significantly Different Findings ($p < 0.05$) Between the Patients in this Study and Sporadic Colon Cancer Patients*

Finding	HNPCC Patients	Sporadic Colon Cancer Patients*
Age of first colon cancer diagnosis	45.6	63.0
Location proximal to the splenic flexure of the colon	69.1%	28.6%
Location in the rectum or sigmoid colon	23.3%	66.3%
Synchronous colon cancer	18.1%	4.8%
Metachronous colon cancer	24.2%	7.7%

* From representative published reports dealing with sporadic colon cancer.[5–7]

easily recognized because it lacks a distinctive clinical marker such as multiple polyps. It is important that physicians caring for patients with colon cancer appreciate its subtle presentation because the treatment for affected individuals is different than sporadic colon cancer and its autosomal dominant inheritance pattern allows the use of Mendelian genetics to make accurate predictions concerning risk for other members of the family. The incidence can be appreciated best if one divides the total colon cancer burden into four types: (1) sporadic, 70–80%; (2) familial, which represents those patients who have at least two first-degree relatives with a history of colon cancer without a clearly definable genetic inheritance pattern, 10–20% (3) hereditary colon cancer of the polyposis variety (FPC), slightly less than 1%; and (4) HNPCC, 5–6%.[4]

The natural history of HNPCC delineated by the data in this study suggests several cardinal features: (1) proximal colonic cancer involvement, (2) increased incidence of synchronous and metachronous colon lesions, (3) early age of onset, and (4) autosomal dominant genetic transmission. Extracolonic adenocarcinomas are associated in some of the families. The relationship is best understood if HNPCC kindreds are divided into two syndromes: (1) Lynch Syndrome I (Hereditary Site Specific Colon Cancer), which is characterized by an increased incidence of colon cancer, only, and (2) Lynch Syndrome II (the Cancer Family Syndrome), which is the same as Lynch Syndrome I with respect to colon cancer but is also associated with an increased risk for selected extracolonic adenocarcinomas that develop at a relatively early age and are inherited integrally (*i.e.*, on the same gene) with the colon cancer. The endometrial cancer in the family depicted in Figure 3 serves as an example. In this study, only female genital cancers were inherited in this fashion. However, breast, pancreas, and other cancers have been reported to act the same way in other families.[4] Once the cardinal features of HNPCC, as well as the relationship to extracolonic carcinomas, are appreciated, it is possible to recognize patients who are members of an affected family and then make appropriate treatment recommendations which, for the colon, are different than one would make for the same patient with a sporadic or familial colon cancer or hereditary colon cancer of the polyposis variety.

Recognition of Patients with Hereditary Nonpolyposis Colon Cancer

A surgeon faced with a patient who is a member of an HNPCC kindred with a newly diagnosed colon cancer will not make a correct management decision regarding the appropriate operative procedure unless the presence of the syndrome is appreciated. Unfortunately, no specific biomarkers are available for screening. Thus, the physician must depend entirely on the patient's family history. A relatively young patient with a proximal colon lesion is the first clue that should arouse suspicion. The next step is to inquire about the family history with specific attention to the presence of an autosomal dominant inheritance pattern and the presence of synchronous and metachronous lesions. An example is provided by examining the pedigree of one of the families in the data base of the current study (Fig. 3). Let us assume that the surgeon is asked to see the patient indicated by the box. He is a 46-year-old man with a newly diagnosed colon cancer. He has a past medical history of two previous colon cancers, one at age 37 and another at age 43. Inquiry concerning his family history reveals that his father and his paternal grandfather both had colon cancer. In addition, colon cancer has developed in three aunts and one uncle on his father's side. Finally, two of his paternal cousins have been affected. The autosomal dominant inheritance pattern is obvious. More detailed questioning will confirm the presence of frequent metachronous lesions, relatively early age of onset, and a proclivity for proximal colon involvement. No other measures are necessary to confirm that this patient is a member of an HNPCC kindred.

Figure 3 also illustrates another important consideration in evaluating patients for the presence of HNPCC. The family is an example of Lynch Syndrome II, which is determined by the inheritance of the endometrial cancer in concert with the colon cancer. Endometrial cancer developed in the patient's aunt (see arrow Fig. 3) at age 45. The chance of this being a random event is small because the incidence of endometrial cancer in the general population is only 3.6%.[1] This, coupled with her relatively young age for the development of endometrial cancer, makes it likely that she harbors the deleterious gene that contains both cancers. Thus, she is at great risk for the development of colon cancer if she lives long enough. It is simply a matter of the endometrial cancer phenotype being expressed before the colonic. For the same reasons, the patient's niece, who developed colon cancer at age 39, is at great risk for endometrial cancer.

Therapy of HNPCC

Treatment considerations for patients who are members of HNPCC kindreds should be divided into three clinical situations: (1) treatment of the patient with a newly diagnosed colon cancer, (2) recommendations for family members as yet unaffected by colon cancer, and (3) recommendations for patients who have had a previous conventional colectomy that is now known to have been inadequate therapy because the HNPCC syndrome has just been identified (see Table 3).

Treatment of a Newly Diagnosed Colon Cancer Patient

On the basis of our data on synchronous and metachronous colon cancer, we recommend a subtotal co-

TABLE 3. *Summary of the Treatment and Surveillance Recommendations for an Individual Known to be a Member of an HNPCC Family*

I. A patient with a newly diagnosed colon cancer:
  (1) Lynch I and II patients:
    A. Subtotal colectomy with ileorectal anastomosis.
    B. Biannual endoscopic evaluation of the remaining rectum.
  (2) Lynch II patients only:
    A. Female genital tract cancers: consider prophylactic TAHBSO at the time of the colectomy. Otherwise, biannual pelvic examination and yearly endometrial aspiration biopsy. ? Ovarian ultrasound.
    B. Individualized surveillance program as determined by the pedigree if the extracolonic cancer is also extragenital.
II. A patient as yet unaffected by cancer:
  (1) Lynch I and II patients:
    A. Biannual occult fecal blood testing beginning at age 20.
    B. Yearly colonoscopy beginning 5 years earlier than the age of onset of the earliest colon cancer in the family.
    C. Prophylactic subtotal colectomy with ileorectal anastomosis for obligate gene carriers.* Biannual endoscopic evaluation of the remaining rectum.
  (2) Lynch II patients only:
    A. Female genital tract cancers: biannual pelvic examination and yearly endometrial aspiration biopsy. ? Ovarian ultrasound.
    B. Individualized surveillance program as determined by the pedigree if the extracolonic cancer is also extragenital.
III. A patient treated by partial colectomy before being recognized as an HNPCC family member:
  (1) Lynch I and II patients:
    A. Biannual occult fecal blood testing.
    B. Yearly colonoscopy.
    C. A completion subtotal colectomy if not totally compliant.*
  (2) Lynch II patients only:
    A. Female genital tract cancers: biannual pelvic examination and yearly endometrial aspiration biopsy. ? Ovarian ultrasound.
    B. Individualized surveillance program as determined by the pedigree if the extracolonic cancer is also extragenital.

* An opinion from a clinical geneticist is urged before proceeding with therapy.

lectomy with ileorectal anastomosis. Because of the propensity of these cancers to involve the proximal colon, sacrifice of the rectum would not be routinely performed. Even the less mutilating mucosal proctectomy, pouch-anal procedures are not believed to be indicated because the incidence of rectal cancer does not justify the added morbidity when compared with ileorectal anastomosis.[8] Of some concern, however, is the concept that by transferring the effluent of the distal ileum from the right colon to the rectum, one might establish the same environment in the genetically susceptible mucosa of the rectum that had previously existed in the right colon. This could result in a high incidence of cancer in the retained rectum.[9] As yet, no data are available to address this question because so few patients are treated correctly with a subtotal colectomy when the initial colon cancer is diagnosed. Since the majority of patients we are now following for HNPCC are being treated with a subtotal colectomy at diagnosis of the first colon cancer, mature data should be available in several years.[10] Currently, frequent endoscopic evaluation of the remaining rectum is all that is recommended.

Patients from Lynch Syndrome II families must also have consideration given to integrally inherited extracolonic cancers. In this study, all of these cancers involved the female genital tract. Therefore, hysterectomy and bilateral salpingo-oophorectomy is recommended at the time of the colectomy. A difficult problem exists in the younger patient, perhaps in her early 30s. Factors such as childbearing desires, osteoporosis, psychological considerations, and the carcinogenic effects of prolonged estrogen replacement therapy complicate the management recommendations. A decision concerning removal of these organs must be individualized for each patient. If hysterectomy and oophorectomy are not performed, a screening program consisting of biannual pelvic examinations with attention to the ovaries and yearly endometrial suction curettage as an office procedure should be begun. The role of screening ovarian ultrasound is currently under investigation.[11]

If the extracolonic cancer is also extragenital, the pedigree must be examined on an individual basis and recommendations made to the family concerning risk. Prophylactic treatment of these organs is usually not practical but an effective surveillance program should be outlined. An opinion from a geneticist in these uncommon families may be in their best interest.

Recommendations for Other Members of the Family as Yet Unaffected by Colon Cancer

The autosomal dominant inheritance pattern of this condition dictates that only 50% of the first-degree relatives in an HNPCC kindred have the cancer gene. In general, prophylactic colectomy is not recommended. It is imperative that an effective surveillance program be established. Our recommendations include biannual fecal occult blood testing and yearly colonoscopy beginning 5 years earlier than the youngest colon cancer occurring in the family, *i.e.*, age 25–30. It is our belief that yearly endoscopy is mandatory because the widely accepted polyp cancer sequence in sporadic cancer may not be applicable to this hereditary cancer syndrome. So called "flat mucosal" cancers have been suggested by patients who have had thorough colon examinations, both operatively and endoscopically, only to present with invasive colon cancer in a period of just a few months.[2]

There are some situations in which the risk for developing cancer approaches 100% and therefore prophylactic surgery is indicated. An example would be a patient from an HNPCC family who relates a history of a parent and a son or daughter who has developed colon cancer. Mendelian genetics dictates that an autosomal dominant gene could not have been passed from the parent to a grandson or granddaughter without being present in the "middle" person (obligate gene carrier). This assumes that the gene was not present in the opposite side of the family and that the development of colon cancer in the parent, grandson, or granddaughter was not a random event. Since the gene has a high degree of penetrance (89%), the risk of developing colon cancer is extremely high.[10] Prophylactic subtotal colectomy with ileorectal anastomosis is recommended in this situation.

In Lynch Syndrome II patients, a surveillance program must also be outlined for selected extracolonic cancer as determined by the individual pedigree. For families with integrally inherited female genital tract cancer, we are currently recommending biannual pelvic examinations and yearly endometrial suction biopsies beginning at the same age as the endoscopy.

Recommendations for Those Individuals Affected by Colon Cancer but Treated before being Recognized as a Member of an HNPCC Family

It is not unusual to see a patient who has had a conventional partial resection for colon cancer in which the significance of the family history was not appreciated. Our data suggest that the risk of developing metachronous colon cancer is 40% by 10 years. At the very least, an aggressive screening program for the remaining colon and the appropriate extracolonic organ(s) (Lynch Syndrome II patients only) must be recommended. Examination of an individual pedigree sometimes discloses a higher rate of metachronous colon cancer than average. In these patients we recommend conversion to subtotal colectomy. This recommendation is also made in any patient who will not be totally compliant with an effective surveillance program.

Conclusion

Construction of a nuclear pedigree in patients with colon cancer allows the use of basic genetic principles to ascertain an autosomal dominant inheritance pattern. HNPCC is confirmed when the autosomal dominant inheritance pattern is found to be coincident with the cardinal clinical features for the colon cancer, namely, early age of onset, proximal involvement, and frequent synchronous and metachronous lesions. Subtotal colectomy with ileorectal anastomosis is the treatment of choice for a patient with a newly diagnosed colon cancer who is a member of an HNPCC kindred. Extracolonic adenocarcinomas are common in some of these families (Lynch Syndrome II), and thereby dictate the need for prophylactic extirpative surgery or at least an intensive surveillance program directed at the specific organs suggested by the pedigree. Members of the kindred who are as yet unaffected by cancer are at a 50% or greater risk, (*i.e.*, obligate gene carriers approach 100% risk). An intensive surveillance program is begun at a young age. Prophylactic surgery is recommended in selective cases. Finally, patients treated for colon cancer with a partial colectomy before it was discovered that they were members of an HNPCC kindred should have their follow-up treatment considered in the light of a 40% chance of metachronous colon cancer developing by 10 years. These treatment recommendations are summarized in Table 3.

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Discussion

DR. CLAUDE H. ORGAN, JR. (Oklahoma City, Oklahoma): I rise to congratulate Dr. Fitzgibbons and his associates for identifying a distinctive subset of colonic neoplasms that have as their characteristics an early age of onset, an autosomal dominant mode of transmission, an excess proximal concentration of these lesions, increasing numbers of synchronous and metachronous lesions, and the possibility of an improved survival.

C. P. Snow has suggested that we are suffering from two coexistent but inadequately communicating cultures: the culture of the clinician and the culture of the basic science investigator (JAMA 1973; 225:617–621).

What is clearly needed for the most effective translation from discovery to practice is not only better communication but a happy cohabitation. Familial colon cancer interfaces both basic science and clinical medicine and offers a method of communication and cohabitation.

A genetic factor has been repeatedly suggested as part of the etiology of colon cancer despite the persistent criticism that such cancer clusters were chance occurrences or the result of shared environmental and dietary influences.

(Slide) This slide confirms the reported kindred manifest in site-specific colon cancer in the absence of familial polyposis dating back to 1956.

I apologize for this being such an active slide, but these are 11 worldwide reports. If you look at the bottom line, you will notice that between 40 and 70% of these cancers are located in the proximal colon (with an average of 67%) and the mean age at onset varies from 29 to 51 years in these 11 worldwide reports with a mean average of 40 years of age. In a majority of instances in which the primary was in the left colon, the metachronous or the synchronous carcinoma was in the cecum.

Dr. Fitzgibbons has appropriately brought to our attention the genetic heterogenicity of these lesions, which is important in the follow-up and subsequent evaluation of these individuals for a long period.

The data he has presented in this paper justify the use of total colectomy with rectal preservation in those cases in which the pedigree analysis and the pathology confirms the presence of hereditary nonpolyposis colonic cancer. These findings must be viewed with the realization that colonic cancer is the most common visceral cancer in the United States.

The development of extended pedigree analysis with tumor and genealogic verification is a long-term, ongoing, dynamic process. Dr. Lynch and his colleagues have shown, with a tenacious group of nurses and social workers, that it is possible to upgrade these pedigree analyses each year.

The observations contained in this report from the familial control center must be viewed cautiously pending the evaluation of much larger cohorts of familial colon cancer with matched controlled individuals inflicted by sporadic colon cancer.

Future epidemiologic surveys of the American Cancer Society's Cancer Commission would be wise to include the familial history in the data base.

I have two questions: (1) are you comfortable using the term "hereditary" in this group of patients since we have not as yet established a single gene-determined etiology, and (2) could this shift from the left to the right side be a national trend as pointed out by Dr. Morgenstern and others?

DR. JEROME J. DECOSSE (New York, New York): Perhaps it should be noted that the concept of subtotal colectomy is not a new one, for it was described by Wangensteen and Lillehei about 1952, then in the context of an isolated large bowel cancer plus additional adenomas present throughout the large bowel.

I would like to interject a word of caution in this regard, perhaps in a few questions to the authors.

I note that they have described over four generations in their pedigrees. That may take them back 100 years. In our experience with this it is difficult to achieve the certainty in records which appears to be required in the diagnoses given in this paper. Could you tell us how you achieve this kind of accuracy?

Secondly, would the author elaborate on the distinctions between familial *versus* hereditary colon cancer, and how this distinction is made, particularly in relationship to the presence or absence of large bowel adenomas, which seems to be a marker for higher risk.

Finally, the author made a statement that colon cancer and endometrial cancer are on the same gene, perhaps because they seemed to segregate together. Does the author have other evidence that this is the case for that is a major statement?

DR. MALCOLM C. VEIDENHEIMER (Burlington, Massachusetts): Like many surgeons, we have performed total abdominal colectomies for cancer of the colon developing in patients under the age of 50. Probably we have been dealing with this subset of patients described in this current paper without fully understanding that we were so doing.

Under normal circumstances, about one third of all specimens removed for cancer of the colon have associated polyp disease in the resected specimen. Like Dr. DeCosse, I ask whether there was such an incidence of associated polypoid disease in the patients described in this paper.

I would like also to caution against the reliance on Hemoccult® testing in this high risk group. Polypoid disease is notorious for not producing occult blood when Hemoccult® testing is performed. I believe that this high risk group should be placed into a surveillance program that mandates colonoscopy unless they already have had a total colectomy and ileorectal anastomosis.

DR. JOHN S. SPRATT (Louisville, Kentucky): I have one comment, and I would like to ask the authors two questions.

The comment is that the left to right shift can be traced to the mid-1960s when double contrast enema and colonoscope became available. In the autopsy studies that antedated that period there were always many neoplasms in the right colon.

Secondly, in Dr. Lynch's group, there was an author of several papers named Albano many years ago whom I unfortunately never met, but he published one very good paper that said that the cancers associated with this syndrome had a much better prognosis. I would like to know if that is still true.

The second question is: does the vigorous follow-up system that they have suggested show any reduction in the chance of dying of colon cancer?

DR. ROBERT J. FITZGIBBONS, JR. (Closing discussion): Dr. Organ, I very much appreciated your comments, especially because I know of your sustained interest in this subject. You asked if we were noting a shift from a left to a right dominance of colonic cancer in these patients. These cancers tend to be confined to the right colon. We have looked at this carefully because in the general population, it is left-sided. Right-sided colon cancer predominance is integral to criteria for HNPCC.

Dr. DeCosse, you cautioned us about the danger of ascribing this to a single gene without biochemical evidence. We are basing our conclusion of a single autosomal dominant gene on extensive medicogenetic investigations by our group and by colleagues throughout the world. In addition, formal segregation analysis (Bailey-Wilson, et al. Genetic Epidemiology 1986; 3:27–38.) has fully supported this assumption. We very much appreciate the fact that there is no biochemical justification. We are currently investigating the molecular basis for this problem.

Dr. Veidenheimer and Dr. DeCosse both asked: what is the relationship of polyps in this syndrome? There are adenomatous polyps associated with this condition occasionally. However, we have been impressed that patients whom we have been following closely in our Hereditary Cancer Institute show a paucity of adenomatous polyps. We believe that the cancer–polyp sequence seen in sporadic colon cancer is not always active in HNPCC and that some of the colonic cancer in the Lynch syndromes are the result of so-called flat mucosal lesions.

Dr. DeCosse asked that I define the difference between familial and hereditary colon cancer. Familial colon cancer includes those families in which two or more first degree relatives have been afflicted with colon cancer, but without a clear-cut vertical transmission pattern consonant with an autosomally dominant inherited factor. In addition, these families do not show early age at onset, multiple primary colonic cancers with increased synchronous and metachronous lesions, or an excess of female genital cancers, as in Lynch syndrome II. Hereditary colon cancer families, on the other hand, show these features, which are striking in our own extended kindreds.

You also asked about how we were able to thoroughly document these 10 families. As Dr. Organ mentioned, we do have an extremely aggressive staff that looks very carefully at these people. In Nebraska, we have the advantage of having a fairly stable population with minimal migration. Documentation has taken place through very thorough review of medical records, autopsy reports, pathological reports, and operative notes on the vast majority of our cases.

Dr. Spratt, you mentioned my late colleague Dr. Bill Albano. Yes, we are indeed still seeing the better prognosis in these patients that he reported when he published his paper. Clearly, these hereditary nonpolyposis colon cancers for some reason have a better prognosis, but the basis for this remains elusive.

Regression of Atherosclerosis by the Intravenous Infusion of Specific Biochemical Nutrient Substrates in Animals and Humans

STANLEY J. DUDRICK, M.D., F.A.C.S.*

Preliminary studies in 400 New Zealand albino rabbits produced a reliable animal model of nutrient-induced atherosclerosis that simulated that observed in humans. Atherosclerosis was then induced in an additional 1600 rabbits in sets of 40 animals each, maintaining plasma cholesterol concentrations between 1000 and 2000 mg/dL for 6–20 weeks. In each set, 10 control rabbits were killed to document baseline atherosclerosis, and the other 30 rabbits were assigned randomly to one of three groups of 10 rabbits. Groups of 10 rabbits were either continued on the atherogenic diet (group I), given standard laboratory rabbit pellets (group II), or infused continuously with specially formulated anticholesterol solutions *via* central venous catheters (group III) for 6 weeks. At autopsy, atherosclerotic lesions consistently involved 85–95% of the aorta in group I. In group II, atherosclerosis was comparable with the baseline control group with no regression. In group III, regression of atherosclerosis by 90–95% was consistently documented. Correlations between plasma amino acids and plasma cholesterol concentrations were established in four humans with severe atherosclerosis to maximize the cholesterol reduction capacity of the amino acid formulation. Infusion of the modified total parenteral nutrition solution induced prompt reduction in plasma cholesterol levels by 40–60% regardless of the initial level and was accompanied by evidence of regression of atherosclerosis after a 90-day infusion therapy period.

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THE ROLE OF CHOLESTEROL in the etiology and pathogenesis of atherosclerosis has been debated by clinicians and investigators for many decades.[1] An elevated plasma cholesterol concentration is certainly not the only cause of, or contributing factor to, coronary heart disease. However, it appears that reducing elevated plasma cholesterol levels will decrease the risk, or is associated with a decreased risk of myocardial infarction secondary to atherosclerotic coronary heart disease.[2,3]

During the past 20 years, as clinical applications of total parenteral nutrition (TPN) have been expanded, it has been documented that plasma cholesterol concentrations decline to low or low normal levels especially in puppies, infants, critically ill malnourished adults, and long-term home TPN patients. However, early attempts to correlate short-term TPN-induced hypocholesterolemia with regression of peripheral vascular disease by our team at the Hospital of the University of Pennsylvania in six patients studied for 1 month were unsuccessful. Subsequently, several patients in our series who had mesenteric infarction of the small bowel secondary to severe atherosclerosis required another abdominal operation after 3–5 years of nourishment entirely by vein. In four of these patients, the previously documented atherosclerosis in the major abdominal vessels had decreased dramatically or was undetectable at intraoperative evaluation. In six such patients in their fifth to eighth decades of life who died for reasons unrelated to their cardiovascular system after 3.5–15 years of home TPN, postmortem examination demonstrated minimal atherosclerosis or disease-free vessels.

Foremost among other workers who observed cholesterol lowering effects of fat-free TPN were Starzl et al.,[4,5] Folkman et al.,[6] and Yamashita et al.[7] who made novel clinical applications of this phenomenon to the management of patients with hyperlipoproteinemia, glycogen storage disease, and familial hypercholesterolemia.

The goals of this series of investigations were to: (1) strictly control nutrient substrate administration in rabbits and humans to determine the maximum dietary potential to reduce plasma cholesterol concentrations while maintaining adequate nutrition; (2) modify existing intravenous nutrient substrate mixtures to maximize

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their cholesterol reducing effects; (3) determine whether these diets, either directly or secondary to induced hypocholesterolemia, could arrest and/or induce regression of atherosclerosis; and (4) determine whether improved cardiovascular function and secondarily improved blood flow to vital tissues would thereby result.

Animal Studies

Preliminary laboratory investigations were done in 400 New Zealand albino rabbits to develop a reliable animal model of dietary-induced atherosclerosis. By systematically altering the fat, cholesterol, and fiber in the oral diet, a special formulation evolved that consistently induced atherosclerotic lesions comparable in composition, distribution, and gross and histologic appearance to those commonly occurring in humans. The atherogenic rabbit diet (Table 1) was subsequently fed to an additional 1600 animals in quantities sufficient to maintain plasma cholesterol levels at approximately 1000 mg/dL without untoward hepatobiliary or gastrointestinal complications. The severity of atherosclerosis in the major vasculature could be estimated by observing the appearance and extent of atheromatous deposits in the blood vessels of the iris. After 6–20 weeks of maintaining hypercholesterolemia, significant atherosclerosis was routinely demonstrated to affect 30–90% of the surface area of the great vessels, respectively; the lesions were histologically indistinguishable from those seen in humans (Figs. 1–3). By 6 months, some animals had myocardial infarctions, strokes, mesenteric vascular occlusions, and peripheral vascular occlusions secondary to severe atherosclerosis involving more than 95% of the surface of the great vessels and major tributaries.

TABLE 1. *Atherogenic Rabbit Diet Formulation**

- Base formula
  - High fiber Purina Labchow 5326†
    - 14.5% protein
    - 1.7% fat
    - 55 ppm cholesterol
    - 42.4% nitrogen-free extract
    - 8.9% ash
    - Water
    - 22.5% crude fiber
      - 40.9% neutral detergent fiber (cellulose, lignin, hemicellulose)
      - 24.6% acid detergent fiber (cellulose, lignin)
  - Additives per kilogram of base formula
    - 900 g fiber
    - 80 g peanut oil
    - 20 g crystalline cholesterol

* Teklad T.D. 82135, Teklad, Inc., Madison, WI.

† Purina Labchow 5326, Purina Mills, Inc., St. Louis, MO.

A large series of experiments was done in sets of 40 rabbits in which plasma cholesterol levels were maintained at approximately 1000 mg/dL in all animals for 4.5 months. Ten animals in each group were killed to determine the gross and histologic extent and character of the atherosclerosis, and the remaining animals in each experiment were assigned randomly to one of three groups of 10 animals each. For the next 6 weeks, group I rabbits continued to be fed the atherogenic diet, group II rabbits were fed standard laboratory rabbit pellets, and

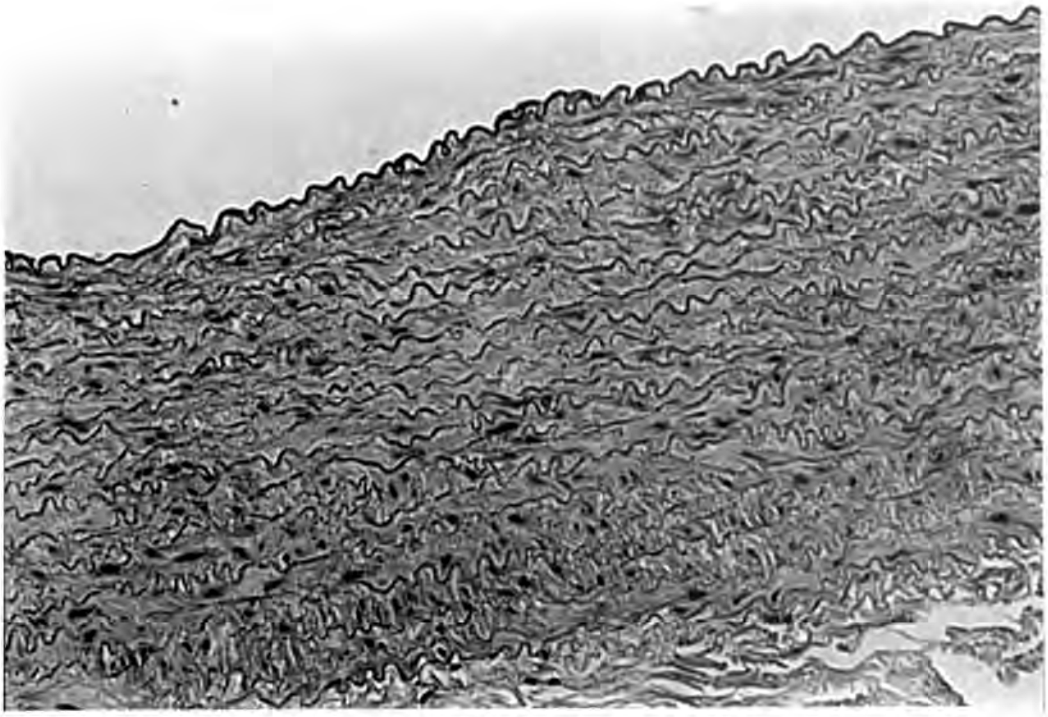


FIG. 1. Intermediate power full-thickness longitudinal section of a normal rabbit aorta. The thin darkly stained convoluted upper border of the specimen represents the entire thickness of the intima. The adventitia is visible in the lower right corner. The media, filled with elastin fibrils, extends between the intima and adventitia.

TABLE 2. *Percentage Composition of Intravenous Amino Acid Formulations*

Amino Acid	Travasol 8.5%*	FreAmine III 8.5%†	Aminosyn 10%‡	Travasol 10%*	FreAmine III 10%†	Novamine 11.4%§	Atheromine 10.3%*
Isoleucine	4.09	6.53	6.61	5.46	6.51	4.83	4.0–10.0
Leucine	5.30	8.53	8.64	6.65	8.59	6.70	5.0–10.0
Lysine	3.56	4.93	4.75	3.79	4.92	5.48	4.5–6.5
Methionine	4.36	4.38	3.23	3.20	4.40	4.25	3.5–5.5
Phenylalanine	4.19	4.21	3.20	4.03	4.18	5.30	4.5–7.5
Threonine	3.95	4.15	5.27	4.21	4.16	5.33	2.0–3.5
Tryptophane	0.98	0.92	0.88	1.05	0.91	1.03	1.0–2.5
Valine	4.39	6.94	8.22	5.90	6.97	6.92	4.0–9.0
Alanine	26.01	9.75	17.25	27.64	9.83	19.78	7.0–16.0
Arginine	5.51	5.57	5.59	5.94	5.57	5.90	9.0–18.0
Histidine	2.38	1.69	1.75	2.78	1.68	3.66	1.5–3.5
Proline	4.09	11.98	9.00	7.05	12.04	6.57	4.5–8.5
Serine	0.00	6.90	4.81	5.67	6.94	4.76	2.5–6.5
Tyrosine	0.27	0.00	0.32	0.29	0.00	0.20	0.0–1.0
Glycine	30.92	22.98	20.50	16.35	23.05	11.68	3.0–8.0
Glutamic acid	0.00	0.00	0.00	0.00	0.00	4.30	3.5–5.5
Aspartic acid	0.00	0.00	0.00	0.00	0.00	2.75	2.0–4.0
Cysteine	0.00	0.24	0.00	0.00	0.25	0.56§	0.0–1.0
Total	100.00	99.71	100.00	100.00	100.00	100.00	100.00

* Baxter Healthcare Corp., Deerfield, IL.
† Kendall-McGaw Laboratories, Irvine, CA.
‡ Abbott Laboratories, North Chicago, IL.
§ Cutter Laboratories, Emeryville, CA.

group III rabbits were fed by continuous central venous infusions either with one of the six commercially available amino acid solutions listed in Table 2 or with specially formulated solutions designed to achieve a maximum plasma cholesterol lowering effect. All amino acid mixtures were administered continuously by pump over 24 hours together with all essential vitamins, minerals, and trace elements and all nonprotein caloric requirements as dextrose. All intravenous solutions were fat free. Blood samples were obtained weekly throughout the 6 months to monitor lipid profiles and standard biochemical and hematologic indices. Serum and urine amino acid profiles were obtained monthly, and all animals had autopsies at the end of the study.

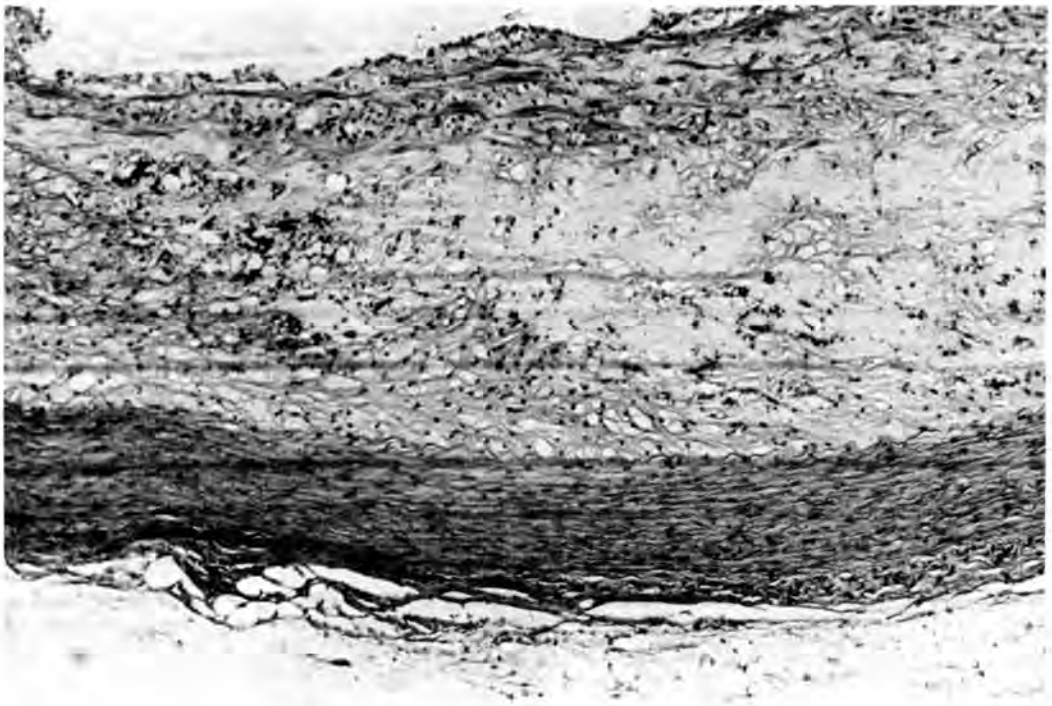


FIG. 2. Low power longitudinal section of the aorta from an animal fed a high-cholesterol diet for 4.5 months. The intima histologically fulfills the criteria of a complicated lesion with: (1) smooth muscle proliferation and expansion of the intima from 1 to 30 cells thick, (2) focal calcification is depicted by the darkly stained calcium deposits, (3) vacuolated appearance of foam cells, and (4) extracellular deposits of cholesterol as cholesterol clefts.

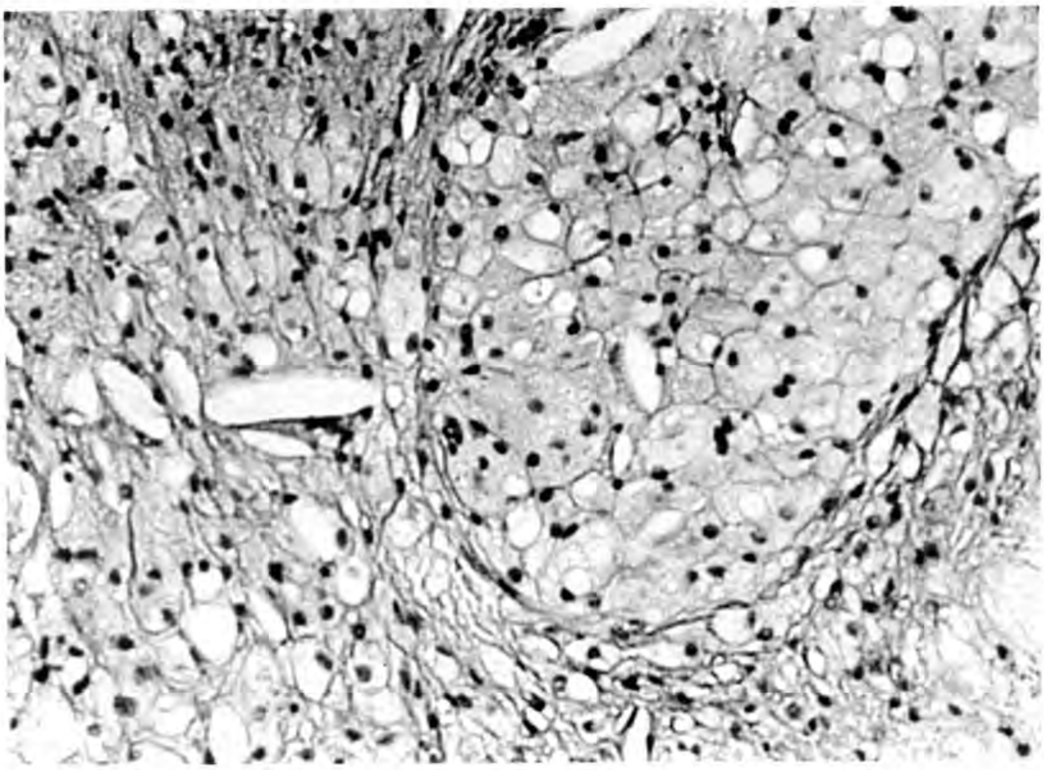


FIG. 3. This high power photomicrograph depicts the deposition of cholesterol and fats both intracellularly (foam cells) and extracellularly (cholesterol clefts).

In group I animals, complex atherosclerotic lesions consistently involved 85–95% of the great vessels. In group II animals, the atherosclerosis was comparable with that in the 4.5-month atherogenic control group with no evidence of significant progression or regression. In group III animals, significant regression of the atherosclerosis was consistently documented by 90–95% clearing of the surface area of the great vessels and major tributaries (Figs. 4–8).

In the first six sets of 40 rabbits, the group III animals received one of six commercially available amino acid solutions (Table 2). After the 6-week intravenous infusion period using these solutions, regression of atherosclerotic lesions varied from minimally detectable to

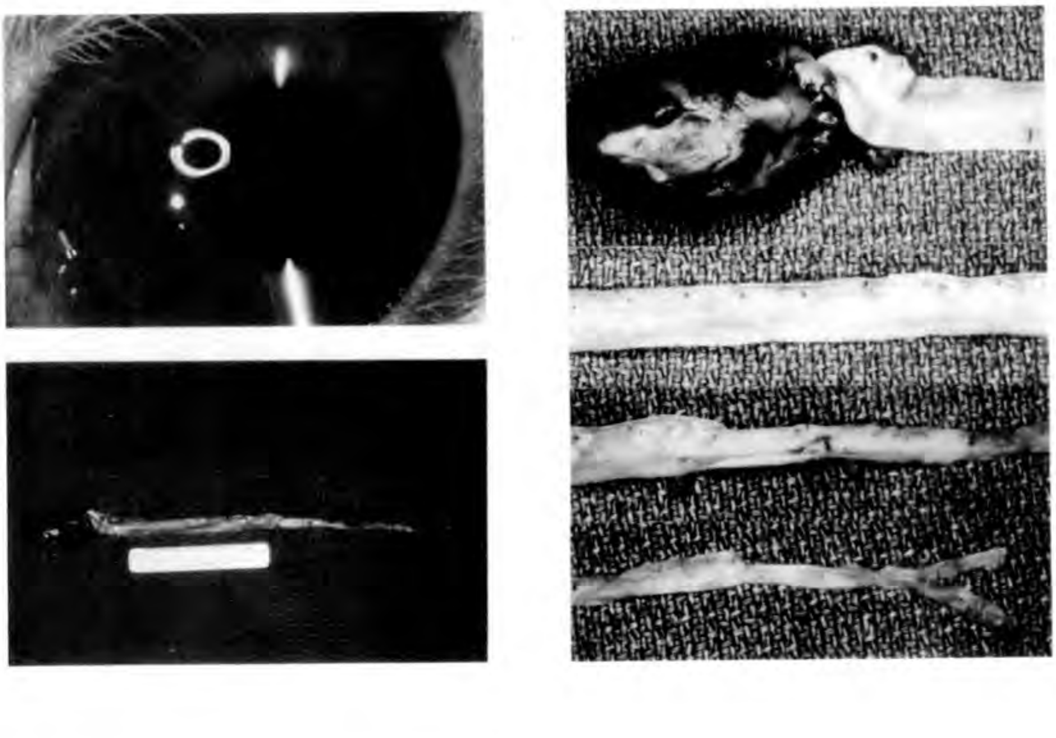


FIG. 4. Composite picture depicting a normal rabbit iris and intimal surface of the aorta with no evidence of atherosclerosis.

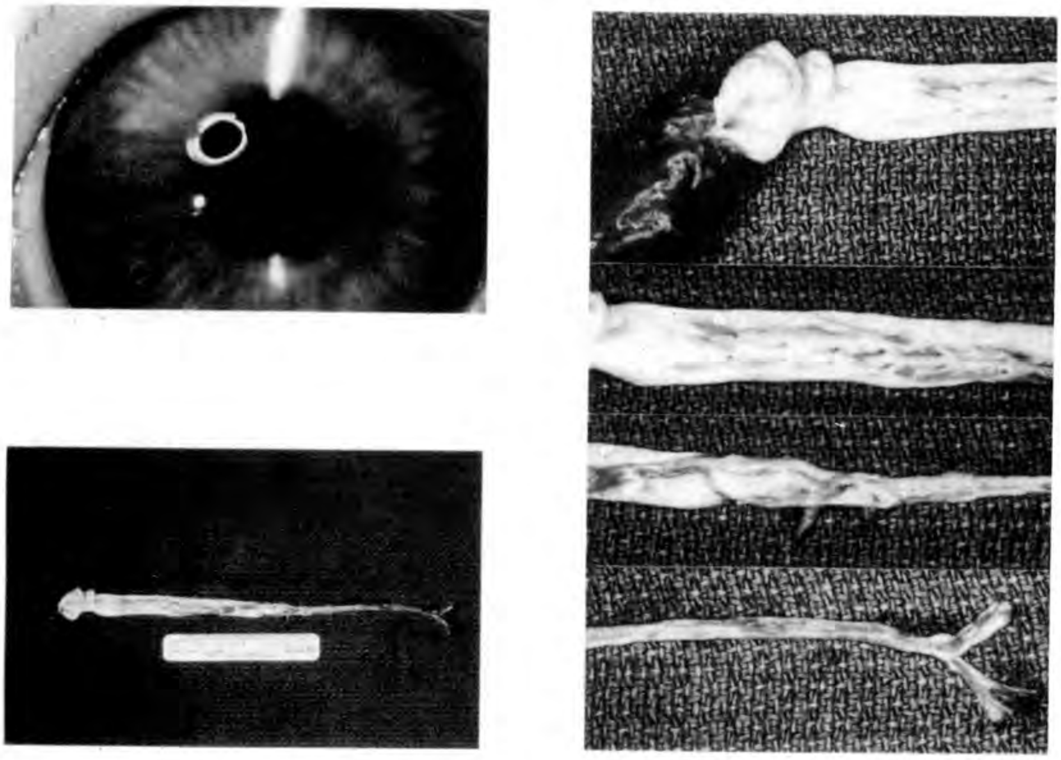


FIG. 5. Composite picture of the iris and aorta in a rabbit fed the high-cholesterol diet for 4.5 months. The lack of pigment in the iris allows direct visualization of the deposition of plaque in the vascular bed, which correlates positively with the atherosclerosis involving 90% of the aorta.

5–10% regression. By correlating plasma and urine amino acid concentrations with plasma cholesterol levels in these animals, changes in the percentages of the individual amino acids were made sequentially in the group III animals and all subsequent sets of rabbits. As a result of these manipulations, a 9.5% amino acid formulation evolved that induced 90–95% regression of the dietary-induced atherosclerosis within 6 weeks. The

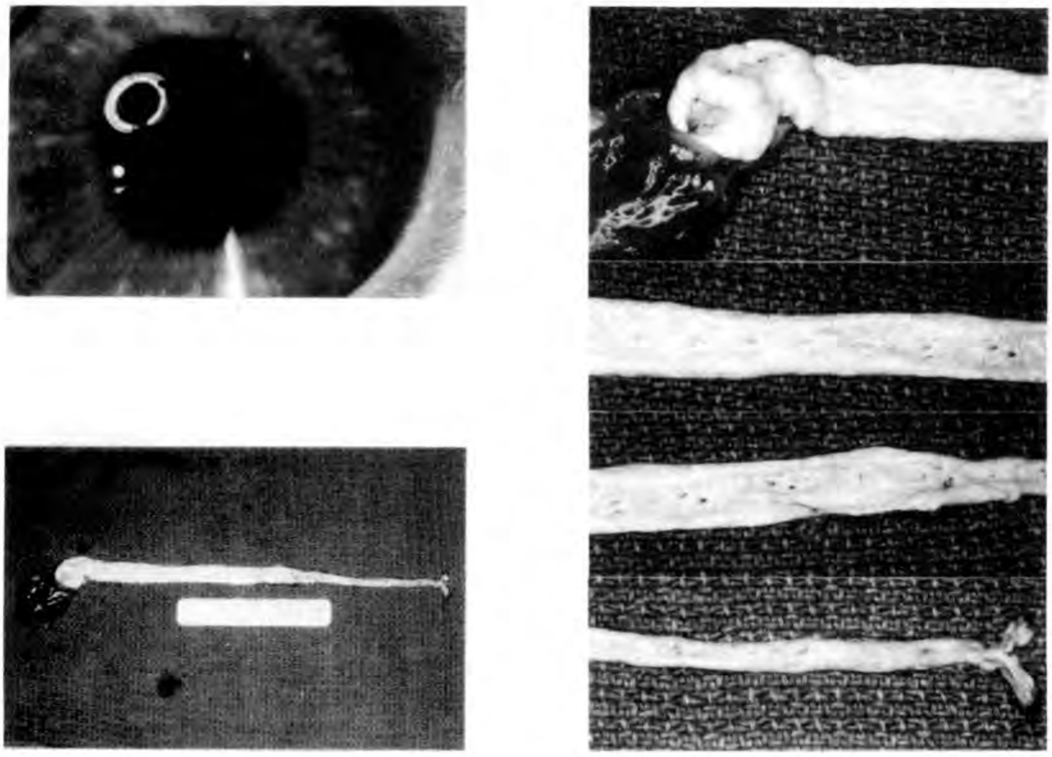


FIG. 6. Composite picture of the iris and aorta in a rabbit fed the high-cholesterol diet for 4.5 months and maintained on the high-cholesterol diet for an additional 6.5 weeks.

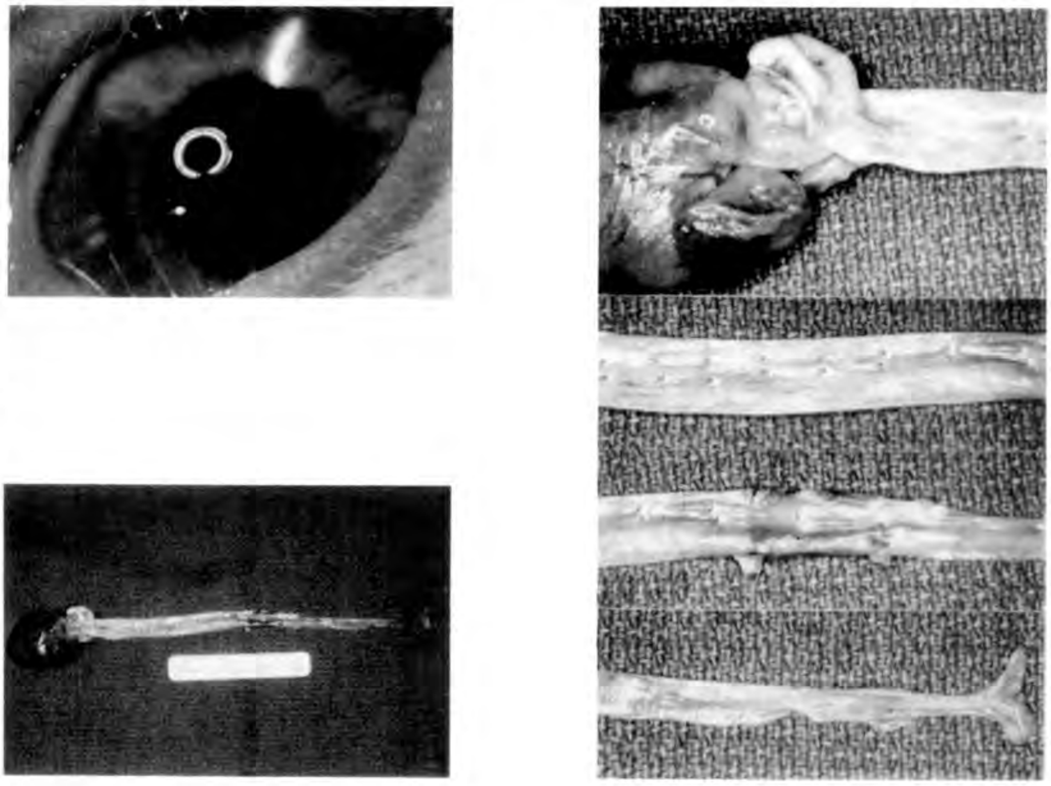


FIG. 7. Composite picture depicting the iris and aorta in a rabbit maintained on the high-cholesterol diet for 4.5 months before switching to low-cholesterol diet rabbit pellets for an additional 6 weeks.

rabbit study was terminated at this point because the data obtained from this model indicated that the maximum atherosclerosis regression potential of the modified TPN solution had been achieved under the experimental conditions. No regression of atherosclerosis has been observed in long-term follow-up studies of 10 rab-

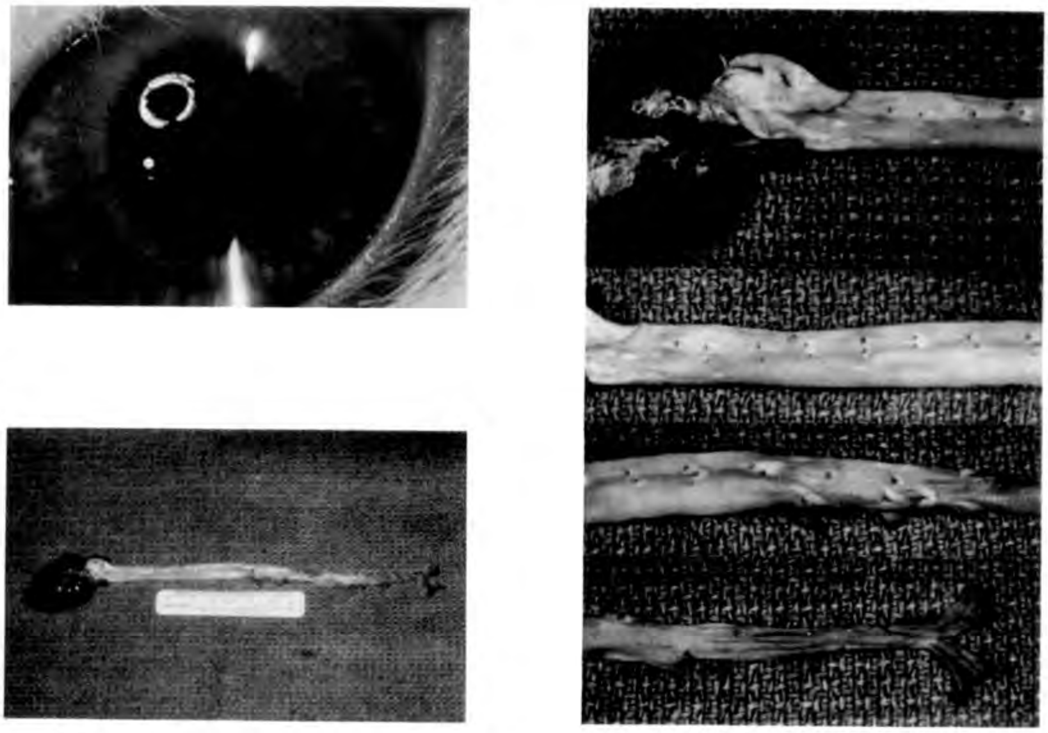


FIG. 8. Composite picture depicting the iris and aorta in a rabbit fed a high-cholesterol diet for 4.5 months and switched to a special mixture of nutrient substrates infused intravenously for an additional 6 weeks. The aortic surface is 95% free of atherosclerosis.

bits that were fed the atherogenic diet for 6 months and then fed the standard laboratory rabbit pellets for up to 2 years.

Patient Studies

Pilot Study: Case 1

A 40-year-old white man with Type IIB hyperlipidemia had an acute anterior myocardial infarction at age 32. After recovery, he was treated with clofibrate, Questran®, and Coumadin®. His plasma cholesterol levels ranged between 500 and 800 mg/dL and his serum triglyceride levels ranged from 800–1000 mg/dL. Dietary manipulation begun in 1977 maintained his plasma cholesterol to levels between 450 and 560 mg/dL. Cardiac catheterization in April 1984, showed 100% occlusion of his right coronary artery and diffuse atherosclerotic disease involving the left anterior descending and circumflex coronary arteries.

Due to the development of progressively increasing severity and frequency of angina pectoris, severe claudication after walking one block, daily dizziness and syncope, and episodic numbness in his extremities related to poor and/or absent pulses in his neck, arms, and legs, he agreed to undergo a 6-month period of intravenous anticholesterol therapy beginning in May 1985. A percutaneous subclavian central venous feeding catheter was inserted into the patient's superior vena cava, and a continuous infusion of the modified TPN solution that had ultimately evolved during the rabbit studies was begun after obtaining baseline biochemical and hematologic studies and instructing the patient in the basic principles and practices of ambulatory home TPN. The patient was allowed absolutely no food by mouth but could drink water *ad libitum*. The patient received no fat during the study, and all nonprotein caloric requirements were provided as dextrose. Since he was approximately eight pounds above his calculated ideal body weight, his formulation for the first few weeks was hypocaloric until he achieved his ideal body weight. Essential vitamins, minerals, and trace elements were provided in accordance with standard home TPN practices. Within 10 days of receiving the initial intravenous anticholesterol diet, his plasma cholesterol level dropped from his preinfusion baseline concentration of 508 mg/dL to 220 mg/dL, representing a greater than 50% reduction. During the 6 months that the patient received the anticholesterol therapy, he had no angina pectoris, dizziness or syncope; his peripheral pulses and perfusion improved greatly; the Doppler blood flow to his left leg increased 250% and to his right leg increased 300%; and the episodic numbness in his hands and feet disappeared completely.

After 4 weeks of therapy, the patient's general health, strength, and feeling of well being improved sufficiently, and he was begun on a graduated monitored treadmill exercise program. During the fifth week of his therapy, he walked 1 mile a day on the treadmill at 1 mile per hour and by the eighth week was walking 3.5–4 miles a day at 3.5 miles per hour without pain or claudication in his legs and with no angina pectoris. During the ninth week of therapy he began to play 18 holes of golf several times a week scoring in the 70s, despite the handicap of having to wear the continuous intravenous infusion apparatus.

During the course of his therapy and study, frequent plasma and urine amino acid concentrations were determined and correlated with his plasma cholesterol level (Fig. 9). At point two, the branched chain amino acids, isoleucine, leucine, and valine, were increased in the formula. At point three, phenylalanine was increased and glycine was decreased in the formula. At point five, alanine was decreased, and glutamic acid and aspartic acid were increased. At point ten, proline and serine were decreased, and at point twelve, arginine was increased, whereas histidine was decreased.

On day 60 at point six, 500 mL of 10% soybean oil emulsion (10% Intralipid, KabiVitrum, Stockholm, Sweden) was infused into the patient over 6 hours, and the plasma cholesterol concentration rose promptly and dramatically more than 100 mg/dL to 365 mg/dL and remained above 300 mg/dL for 1 month. At that point 500 mL of 20% soybean oil emulsion (20% Intralipid, KabiVitrum) was infused over 6 hours, and the plasma cholesterol level again rose significantly but not as high nor as persistently as the initial infusion of the 10% soybean oil infusion. However, the persistent adverse effects on plasma cholesterol levels after infusions of such relatively small amounts of fat emulsion are obvious, dramatic, and disturbing.

Between days 140 and 150, the plasma concentration of arginine was approximately 100 μmol/L, and the urine concentration of arginine was approximately 40 μmol/L (Fig. 10). Because this represented the lower limit of normal for plasma arginine concentration, the dosage of arginine in the infusion mixture was doubled for the next 10 days. This resulted in a rise in the plasma amino acid concentration of arginine to approximately 200 μmol/L, the usual upper normal limit, whereas urine excretion of arginine increased. Concomitantly, the plasma cholesterol level dropped dramatically from 310 mg/dL to 230 mg/dL. At this point, the arginine dosage in the infusion mixture was tripled with essentially no change in plasma concentration of arginine, a dramatic increase in urinary excretion of arginine, and essentially no change in plasma cholesterol concentration. This sequence of events illustrates the manner in which the dosages of the various amino acids in the anticholesterol formulation were derived. All other numbers in Figure 9 represent changes in dextrose calories in response to changes in the patient's body weight and activity.

The significant changes in plasma apolipoprotein B and triglyceride concentrations are illustrated in Figures 11 and 12.

Coronary angiography after the therapy indicated improved flow in the previously completely blocked right coronary artery and increased diameter and flow in the tributaries of the left coronary artery with the development of increased collateral coronary artery circulation, myocardial perfusion, and cardiac performance (Figs. 13 and 14). Coronary arteriographic analysis using computerized quantitative angiography[8] (Figs. 15 and 16) indicated regression of coronary atherosclerosis by an increase in the diameter in one of the branches of the left coronary artery from 1.19 mm before therapy to 1.30 mm after therapy and an increase in cross-sectional area from 1.12 mm^2 before therapy to 1.27 mm^2 after therapy. Coronary flow reserve increased from 3.6 to 4.2, consistent with the disappearance of his angina pectoris. These data assume even greater potential significance considering that the baseline angiography was performed more than 1 year before the initiation of the anticholesterol therapy and that the patient's continuing symptomatic deterioration during that interval indicated further progression of his coronary atherosclerosis during that year.

To date, the patient is 2 years post-initiation of his anticholesterol therapy and 18 months post-completion of his therapy. He has remained completely free of his initial presenting signs and symptoms, has returned to gainful employment as a Computer Systems Analyst, engages in normal physical activity without limitations, plays golf regularly, and enjoys a feeling of good health and well being.

Home TPN Patients

To determine the extent of the increased effectiveness of the anticholesterol amino acid formulation (Atheromine, Baxter Healthcare Corp., Deerfield, IL) in lowering plasma cholesterol compared with the standard amino acid formulations used in home TPN, 30 patients with short bowel syndrome who had been receiving one of the six commercially available amino acid formulations for 4 months to 9 years were studied. The Atheromine solution that had evolved during the pilot patient

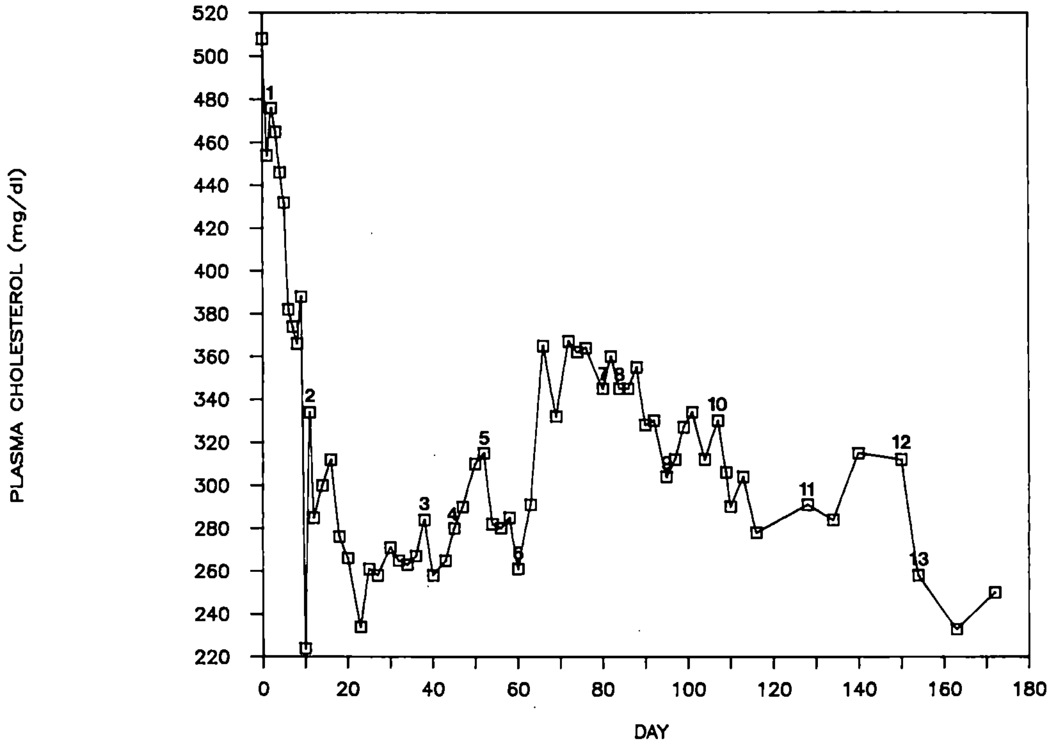


FIG. 9. Plasma cholesterol levels during 6 months of anticholesterol therapy. Numbered points denote significant changes in the components of the formula.

study was substituted for the usual amino acid formula in each of the 30 patient volunteers for 7 days while monitoring plasma cholesterol levels daily. The upper and lower limits of the plasma cholesterol concentrations determined daily for these 30 patients are shown in Figure 17. Prompt reductions in plasma cholesterol

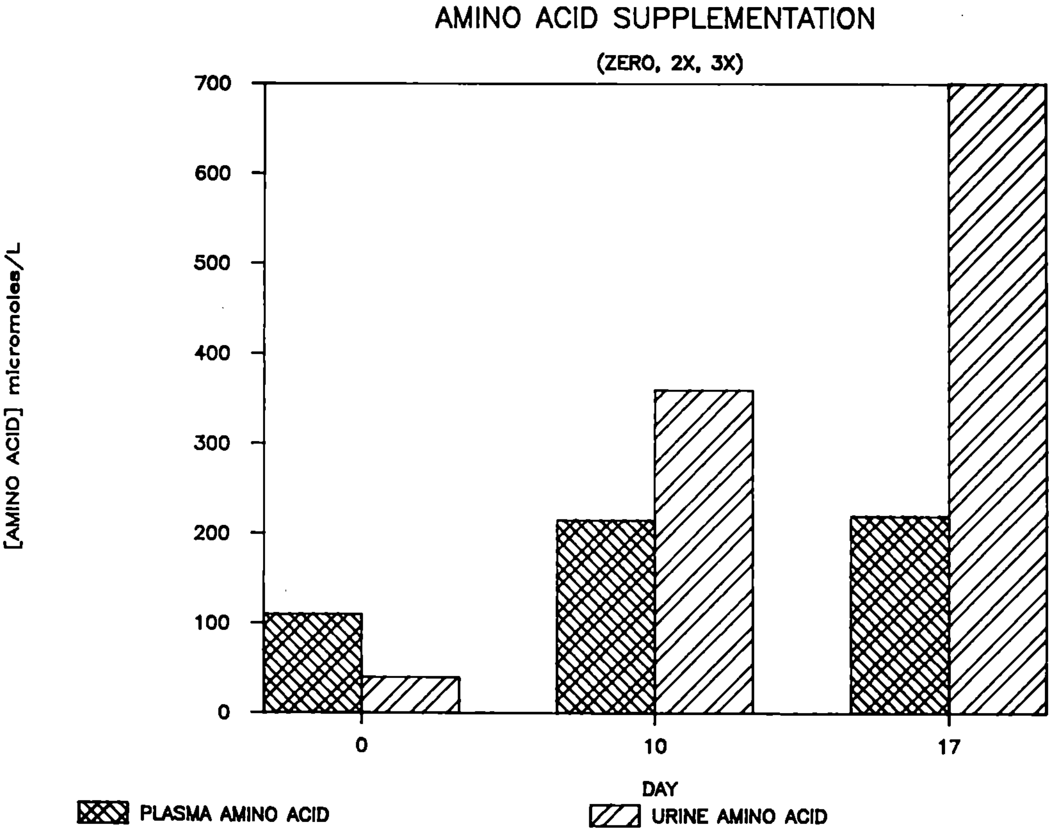


FIG. 10. Relative changes in plasma and urinary arginine levels with changes in the intravenous solution mixture.

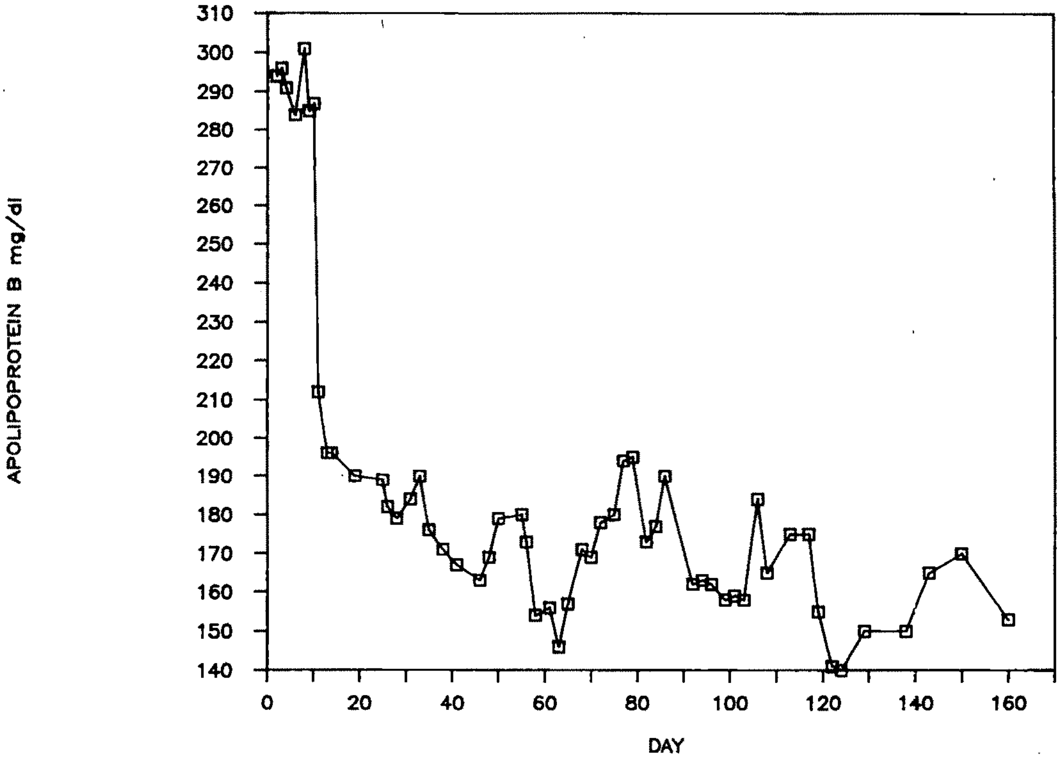


FIG. 11. Alteration of plasma apolipoprotein B levels during 6 months of anticholesterol therapy.

concentrations by 40–60% occurred in all patients regardless of the initial baseline value or the amino acid mixture that had been infused during their standard home TPN regimen. In one patient in whom the baseline cholesterol level was 168 mg/dL, a 58% drop in plasma cholesterol to 70 mg/dL occurred in 7 days.

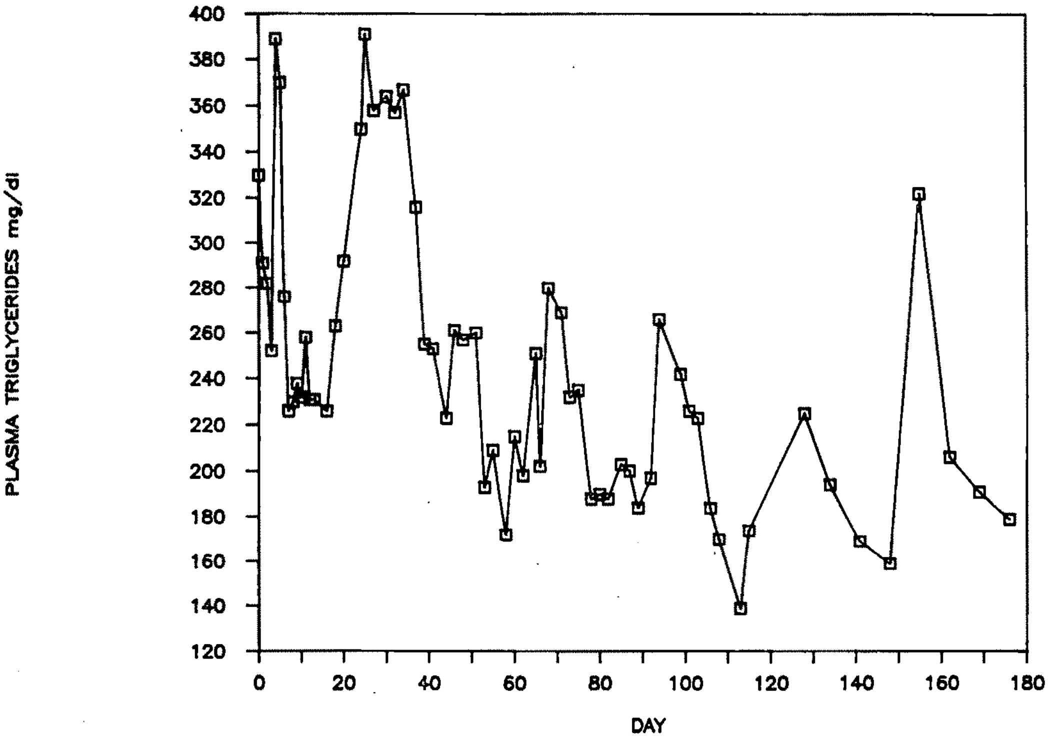


FIG. 12. Alteration of plasma triglyceride levels during 6 months of anticholesterol therapy.

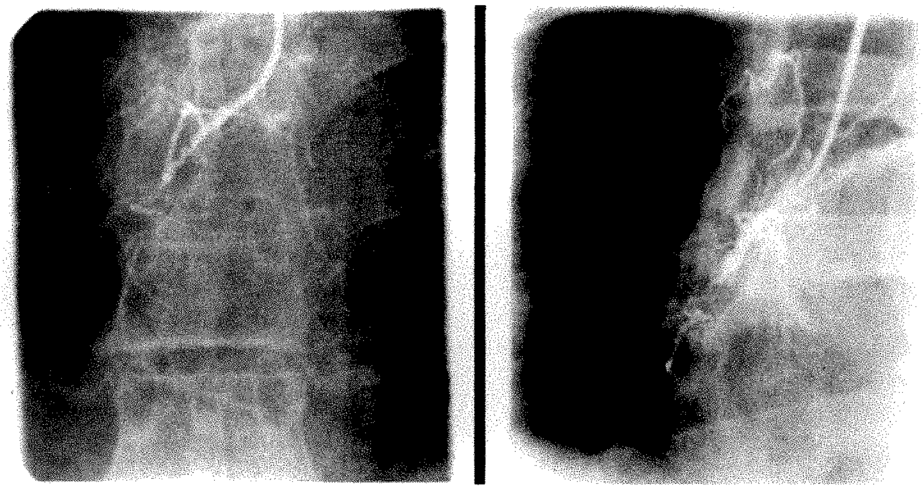


FIG. 13. Angiography shows complete blockage of the right coronary artery before treatment (*left*). Improved flow through the right coronary artery and greatly increased collateral blood flow occurred after therapy (*right*).

Even more dramatic and remarkable was a drop in plasma cholesterol from an already low value of 85 mg/dL by 65% to 30 mg/dL in 7 days.

Case 2

A 55-year-old man with severe coronary artery disease had a myocardial infarction in 1963 at the age of 31. A second myocardial infarction occurred in 1977 and required emergency coronary bypass to five vessels.

Recurrent, persistent angina pectoris developed in March 1985, and in December 1985, he had a third myocardial infarction. Before intravenous anticholesterol therapy, the patient had disabling crushing anterior chest pain 4–5 times per day, even at rest. Cardiac catheterization in 1985 showed three-vessel coronary artery disease with occlusion of the right coronary artery, extensive disease in the left anterior descending coronary artery, occlusion of a large marginal branch of the circumflex coronary artery, and occlusion of all of his bypass grafts with the exception of the left anterior descending graft, which was functioning poorly.

The patient denied angina pectoris after the first two days of anticholesterol therapy with the exception of one mild episode that occurred while riding a bicycle in 30-degree weather against a 45 mph wind for 2.5 miles, a great increase over his usual level of exertional activity.

His medications before anticholesterol therapy included Procardia®, Norpace®, Lanoxin®, Tenormin®, aspirin, nitroglycerin, and nitropaste. At the completion of 90 days of anticholesterol therapy, the patient's only cardiac medication was Lanoxin, and he denied chest pain despite a greatly increased level of physical activity. His initial plasma cholesterol level of 218 mg/dL declined by 39% to a low value during therapy of 123 mg/dL.

His follow-up evaluation included cardiac catheterization and quantitative coronary angiography, which documented an improvement in coronary flow reserve (CFR) from 1.0 to 2.3, an improvement of 130% (Figs. 18–20). Additionally, a pretherapy thallium treadmill test showed a perfusion defect involving the anterolateral, apical, and inferior segment of the left ventricle that did not show any evidence of reperfusion at rest. The post-therapy thallium treadmill test showed resolution of the perfusion defect in the anterolateral segment of the left ventricle. Stress defects and redistribution abnormalities in the apical posterior, lateral, and inferior segments of the left ventricle were not as severe as the pretreatment examination. There was definite evidence for improvement of perfusion of the left ventricle.

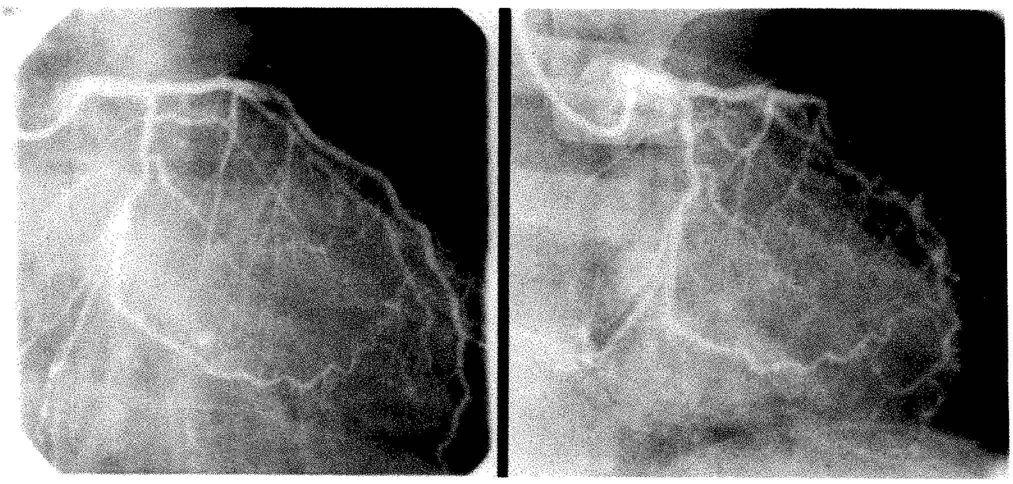
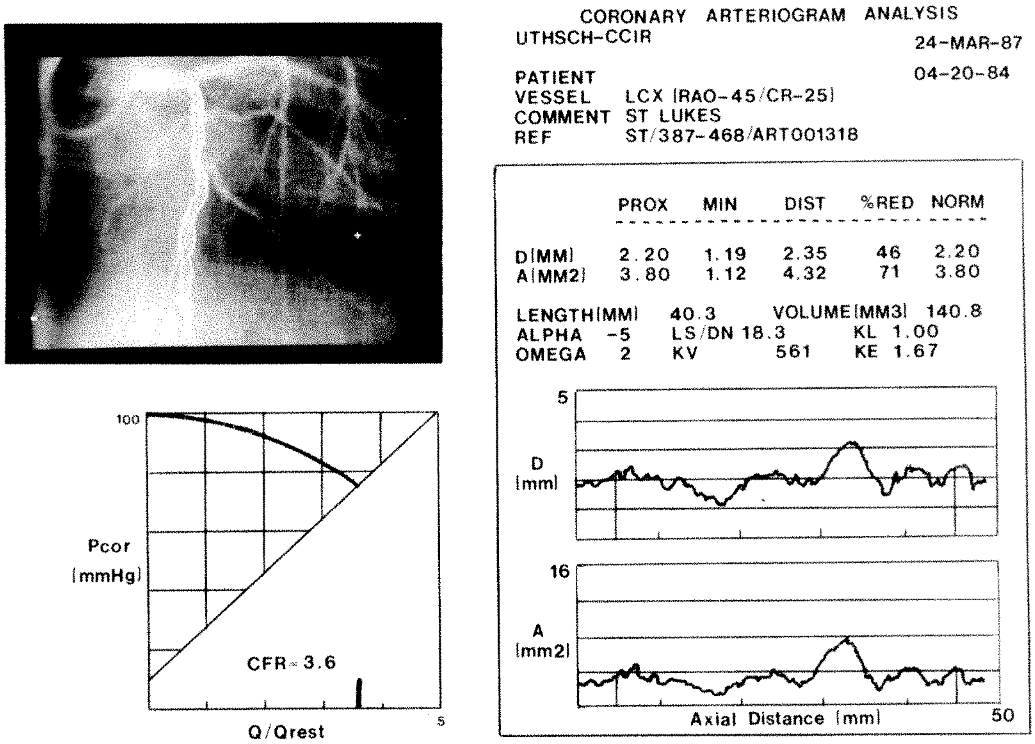


FIG. 14. Increased diameter and blood flow through the left anterior descending and circumflex coronary arteries occurred after therapy (*right*) compared with the pretreatment angiogram (*left*). Improved collateral circulation between the right and left coronary systems can be seen in the left lower quadrant of the right photograph.



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CORONARY  ARTERIOGRAM  ANALYSIS
UTHSCH-CCIR                          24-MAR-87

PATIENT                              04-20-84
VESSEL    LCX (RAO-45/CR-25)
COMMENT   ST LUKES
REF       ST/387-468/ART001318

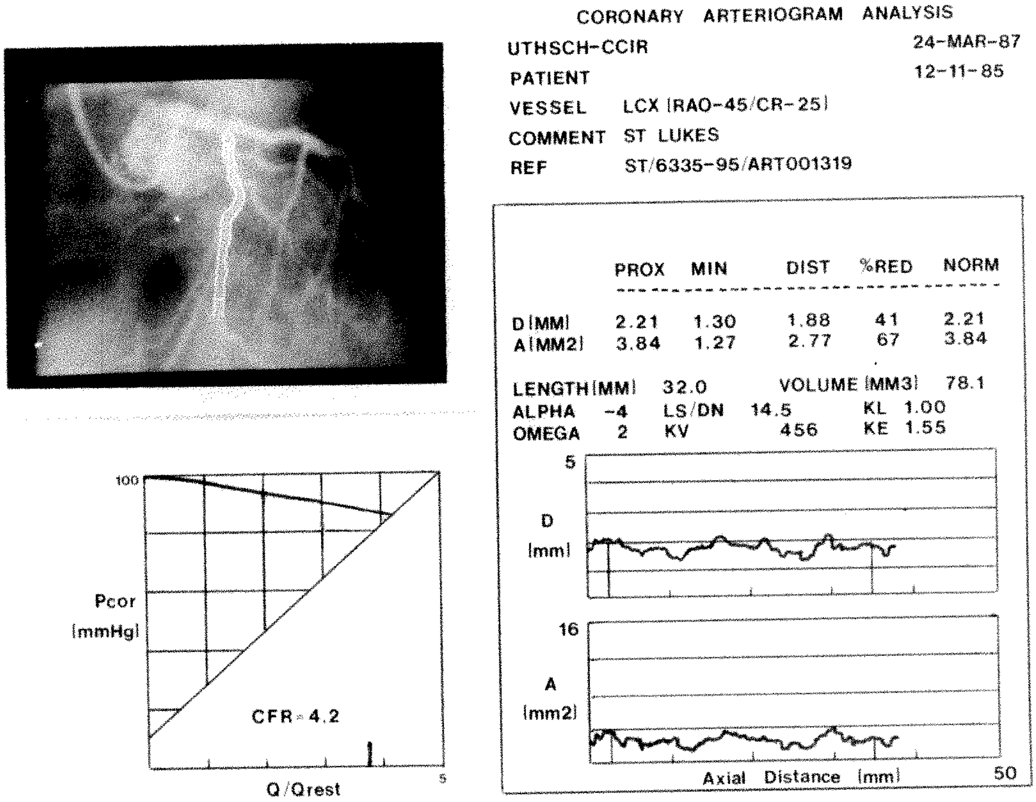
           PROX    MIN     DIST    %RED   NORM
           ---------------------------------------
D(MM)      2.20    1.19    2.35     46    2.20
A(MM2)     3.80    1.12    4.32     71    3.80

LENGTH(MM)    40.3      VOLUME(MM3)  140.8
ALPHA   -5    LS/DN 18.3      KL  1.00
OMEGA    2    KV        561   KE  1.67
```

FIG. 15. Quantitative coronary angiography showing restricted coronary flow reserve of 3.6 before therapy.

Case 3

A 45-year-old previously healthy white man had an inferior wall myocardial infarction that was complicated by ventricular fibrillation from which he was successfully resuscitated. Cardiac catheterization demonstrated a 50% narrowing of the midlateral anterior descending coronary artery, a 50% narrowing of the circumflex artery, and a normal right coronary artery. Despite treatment with an extremely low-fat, low-cholesterol diet and anticholesterol drugs, including nicotinic acid and cholestyramine, he was unable to decrease his plasma cholesterol level below 250 mg/dL.



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CORONARY  ARTERIOGRAM  ANALYSIS
UTHSCH-CCIR                          24-MAR-87
PATIENT                              12-11-85
VESSEL    LCX (RAO-45/CR-25)
COMMENT   ST LUKES
REF       ST/6335-95/ART001319

           PROX    MIN     DIST    %RED   NORM
           ---------------------------------------
D(MM)      2.21    1.30    1.88     41    2.21
A(MM2)     3.84    1.27    2.77     67    3.84

LENGTH(MM)    32.0      VOLUME(MM3)   78.1
ALPHA   -4    LS/DN   14.5    KL  1.00
OMEGA    2    KV        456   KE  1.55
```

FIG. 16. Repeat quantitative coronary angiography showing 16% improved coronary flow reserve to 4.2 after therapy secondary to increased diameter and cross-sectional area of the artery.

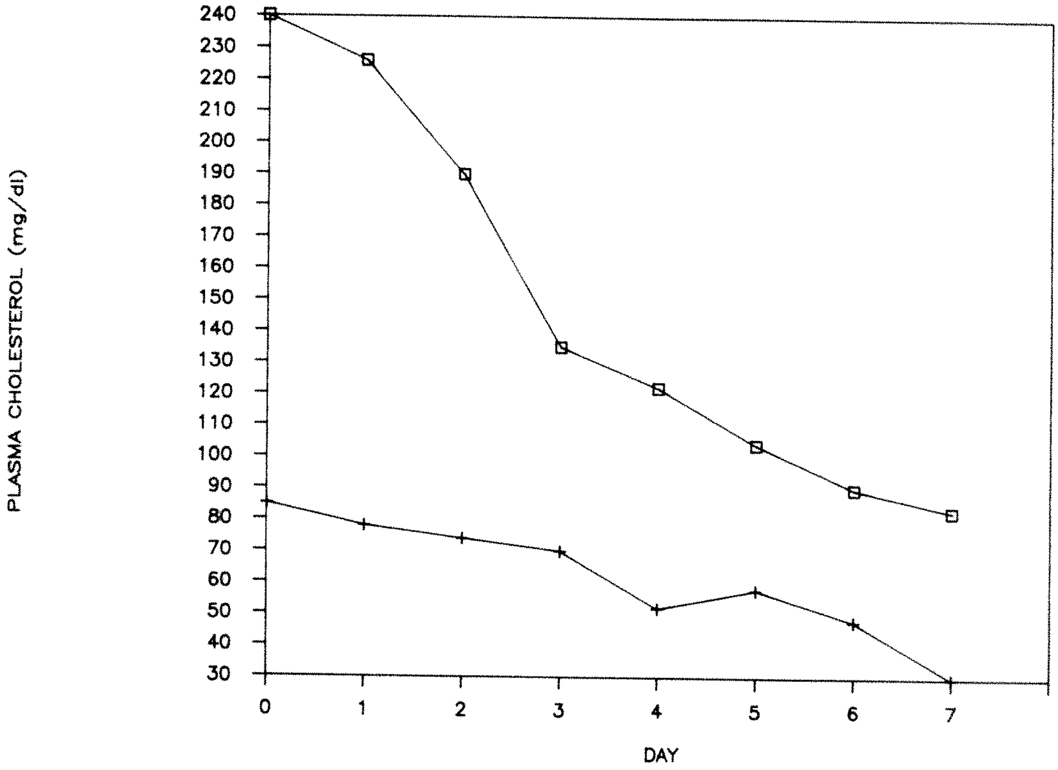
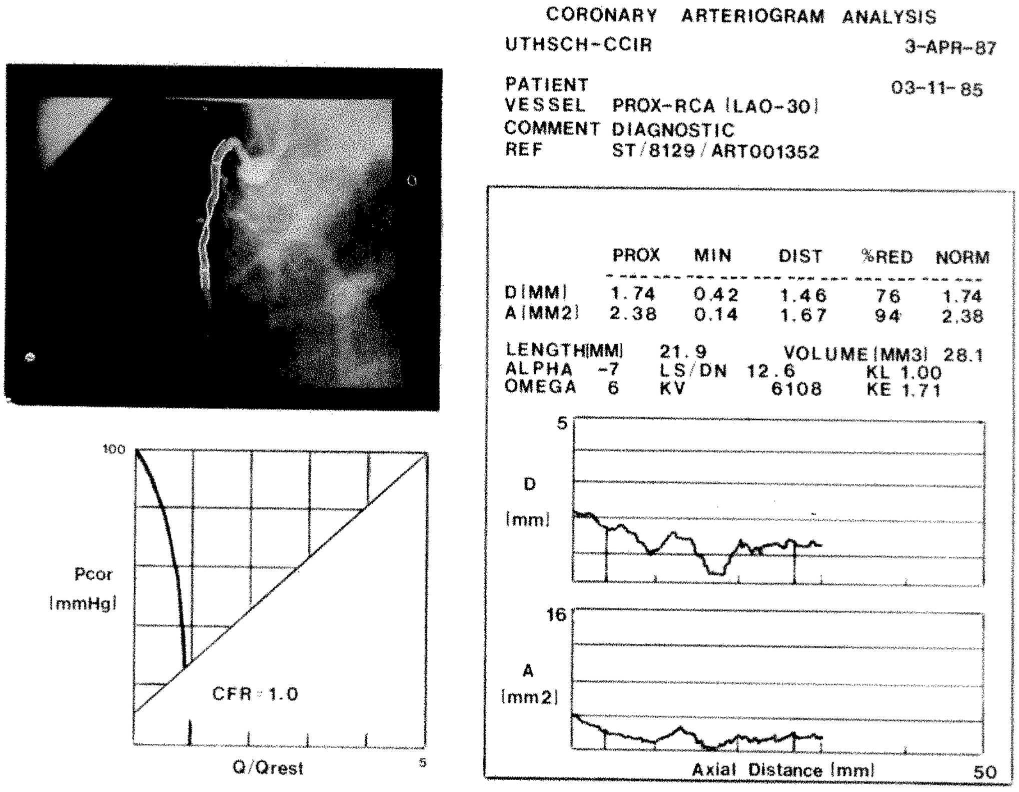


FIG. 17. Upper (☐) and lower (+) levels of plasma cholesterol levels in home TPN patients (N = 30) during the first week of therapy.

During 90 days of intravenous anticholesterol therapy, he lost approximately 1 pound and could be weaned from his cardiac medications (nifedipine and timolol). His plasma cholesterol declined 64% to a low level of 90 mg/dL.

Case 4

A 55-year-old white man with a history of recurrent coronary artery disease and several previous myocardial infarctions initially developed



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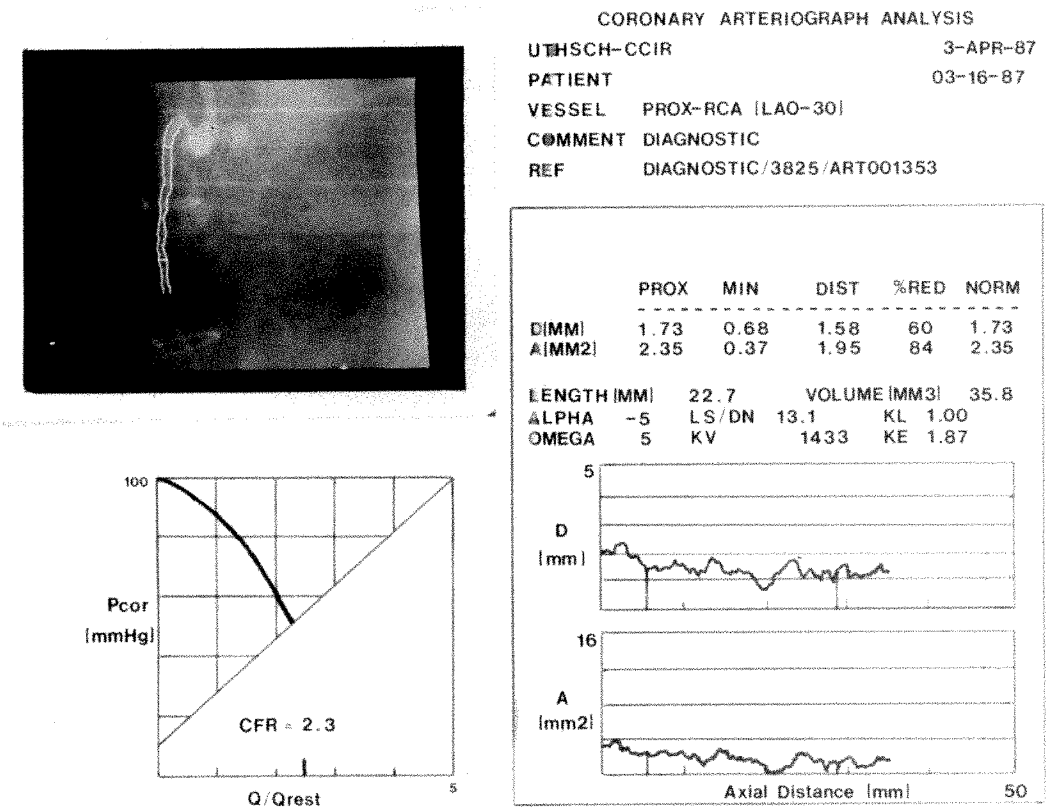
    CORONARY  ARTERIOGRAM  ANALYSIS
UTHSCH-CCIR                          3-APR-87

PATIENT                              03-11-85
VESSEL   PROX-RCA (LAO-30)
COMMENT  DIAGNOSTIC
REF      ST/8129/ART001352

            PROX   MIN    DIST    %RED  NORM
            ----------------------------------
D(MM)       1.74   0.42   1.46     76   1.74
A(MM2)      2.38   0.14   1.67     94   2.38

LENGTH(MM)     21.9        VOLUME(MM3) 28.1
ALPHA   -7     LS/DN  12.6        KL 1.00
OMEGA    6     KV          6108   KE 1.71
```

FIG. 18. Severely compromised coronary flow reserve before initiation of Atheromine therapy secondary to greatly decreased diameter and cross-sectional area of the right coronary artery.



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        CORONARY ARTERIOGRAPH ANALYSIS
UTHSCH-CCIR                           3-APR-87
PATIENT                               03-16-87
VESSEL    PROX-RCA (LAO-30)
COMMENT   DIAGNOSTIC
REF       DIAGNOSTIC/3825/ARTOO1353

           PROX    MIN     DIST    %RED   NORM
           ---------------------------------
D(MM)      1.73    0.68    1.58     60    1.73
A(MM2)     2.35    0.37    1.95     84    2.35

LENGTH (MM)    22.7      VOLUME (MM3)   35.8
ALPHA    -5    LS/DN   13.1       KL   1.00
OMEGA     5    KV          1433   KE   1.87
```

FIG. 19. Marked improvement in coronary flow reserve in right coronary artery after 3 months of Atheromine therapy with significantly increased diameter and cross-sectional area of the previously narrowed segment.

angina pectoris in 1971. Cardiac catheterization showed significant coronary artery disease for which he had an internal mammary coronary bypass (Weinberg procedure). In 1980, he had a myocardial infarction, and recurrent and persistent angina pectoris developed in 1981. At that time a second cardiac catheterization documented significant recurrent disease. He had saphenous vein aorta coronary bypass

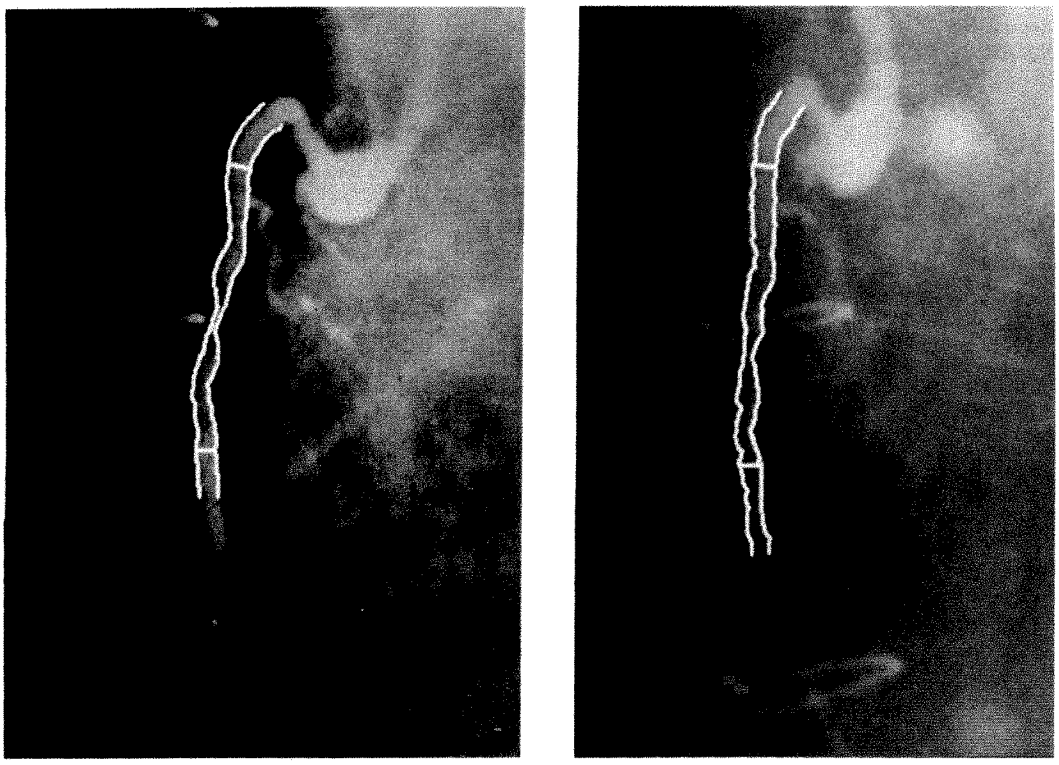

FIG. 20. Enlargement of right coronary angiograms before (*left*) and after (*right*) therapy demonstrating computer augmented vascular outlines.

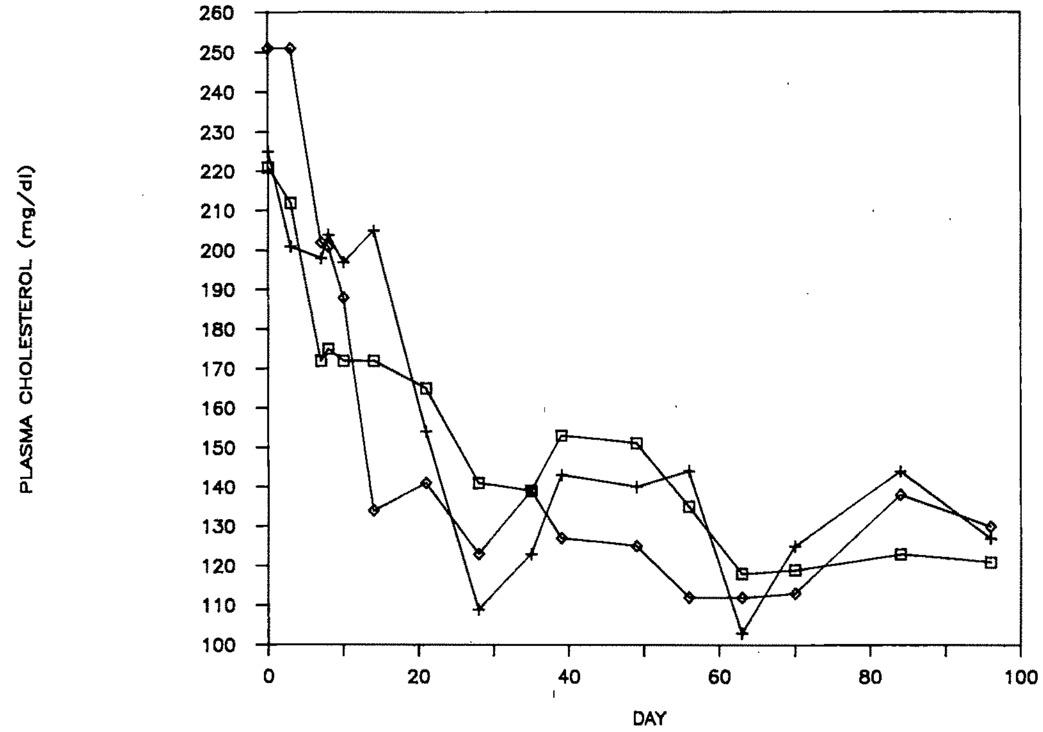

FIG. 21. Total plasma cholesterol levels of three patients during 90 days of Atheromine therapy.

to three vessels with improvement for approximately 2 years until the development of recurrent chest pain primarily associated with exercise. He had cardiac catheterization again in 1983, which showed global hypokinesis with an ejection fraction of 26%, a totally obstructed left anterior descending and distal circumflex coronary artery, and significant disease of the distal right coronary artery.

His angina pectoris became progressively severe over the subsequent 3 years, and at the time of pretreatment evaluation he was having chest pain 4–5 times per day requiring nitroglycerin for relief. He could walk only 2 miles at a slow pace without the development of chest pain. His pretreatment medications included Procardia, Corgard®, and nitroglycerin.

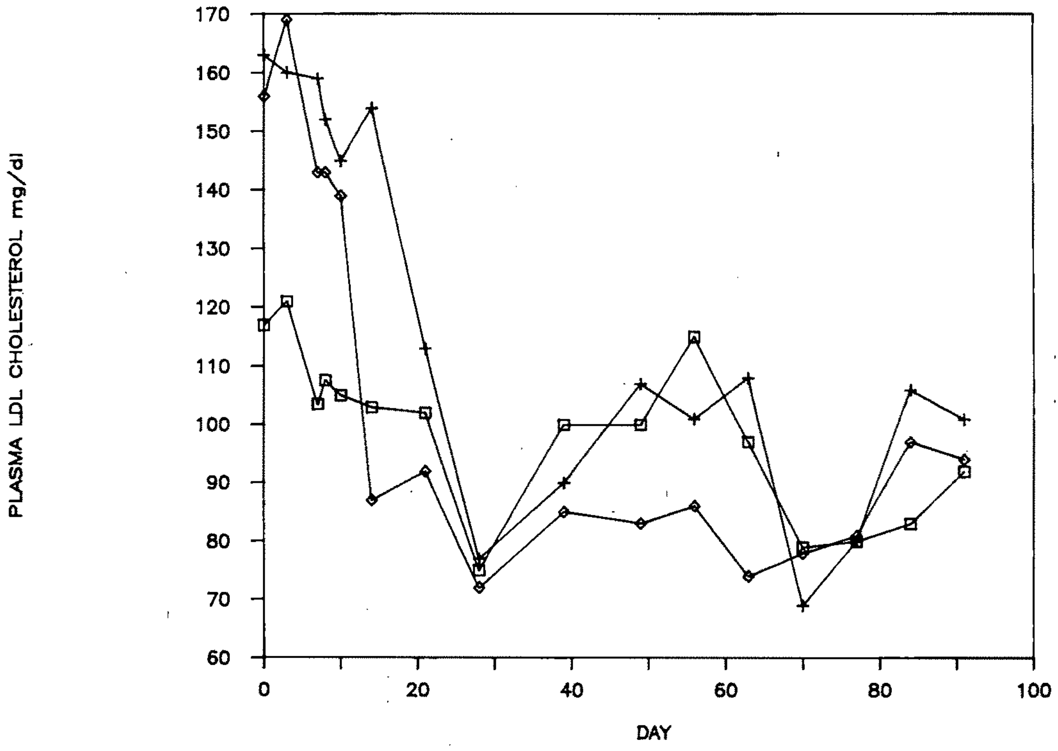

FIG. 22. Plasma VLDL cholesterol levels of three patients during 90 days of Atheromine therapy.

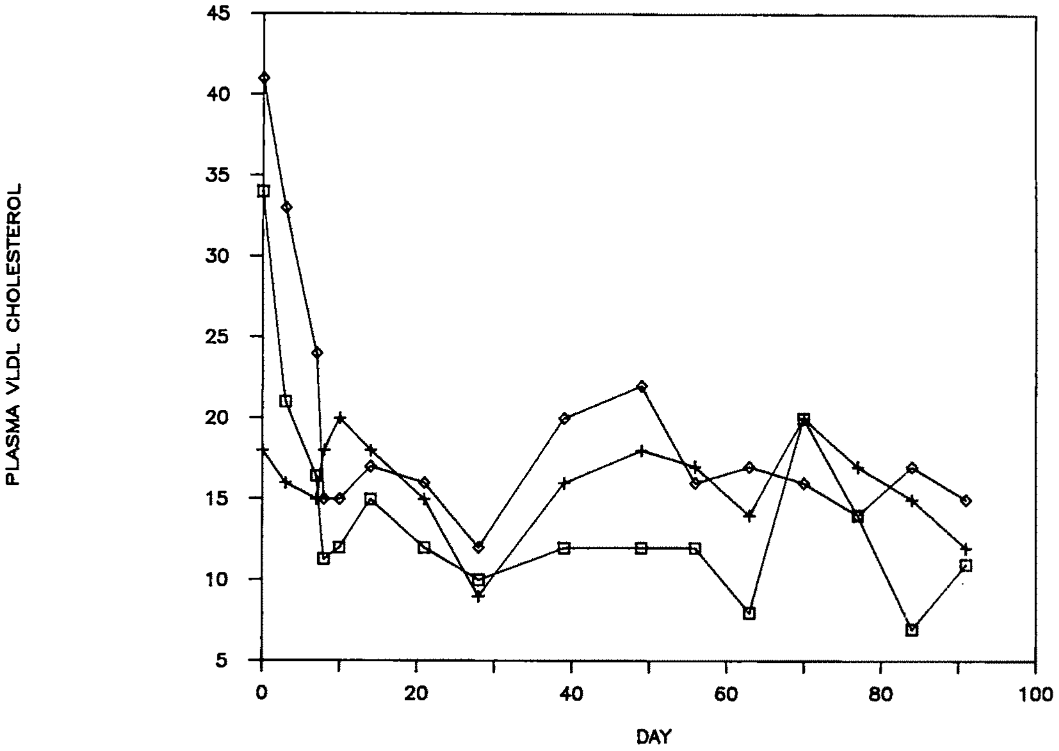

FIG. 23. Plasma LDL cholesterol levels of three patients during 90 days of Atheromine therapy.

After starting anticholesterol therapy, he had no further episodes of angina pectoris despite the development of a subclavian vein thrombosis necessitating placement of a second Hickman catheter and the development of a small bowel obstruction secondary to adhesions that required laparotomy. He lost 16 pounds during the 90-day treatment period and was able to reduce his cardiac medications by 50%.

His initial plasma cholesterol level of 252 mg/dL declined by 66.7% to a low of 84 mg/dL.

His pretreatment positive thallium treadmill test remained positive post-treatment; however, he was able to achieve a 25% higher heart rate during his post-treatment examination. Follow-up cardiac catheterization showed generalized severe coronary atherosclerosis with complete

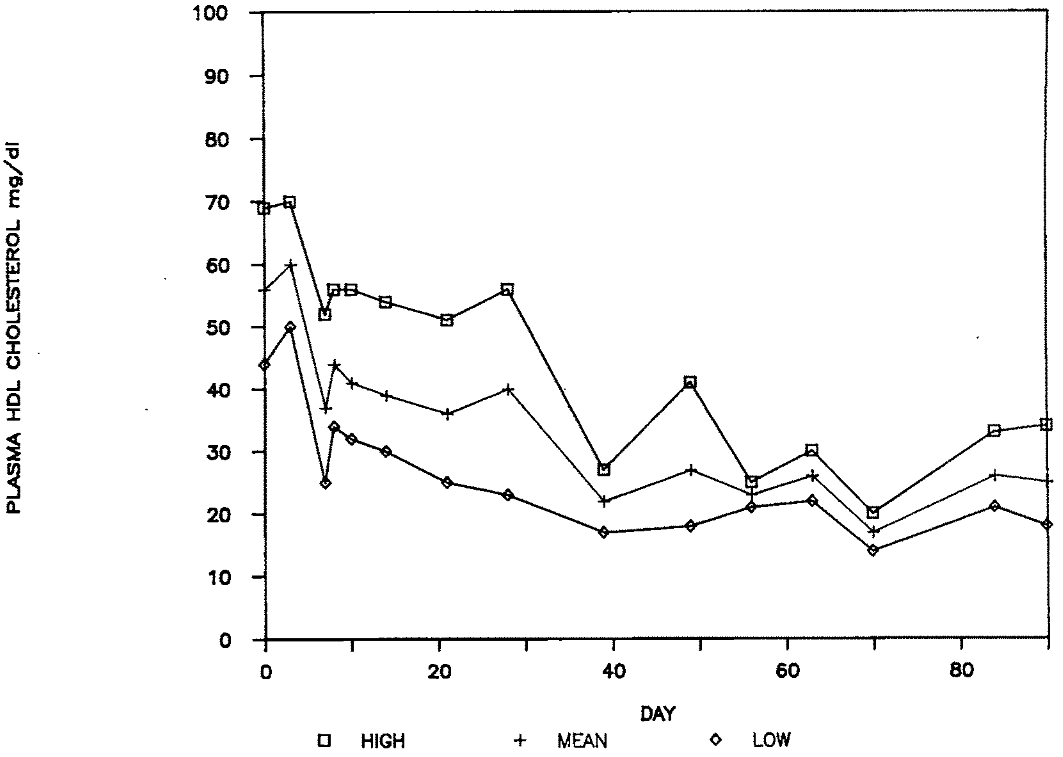

FIG. 24. Plasma HDL cholesterol levels of three patients during 90 days of Atheromine therapy.

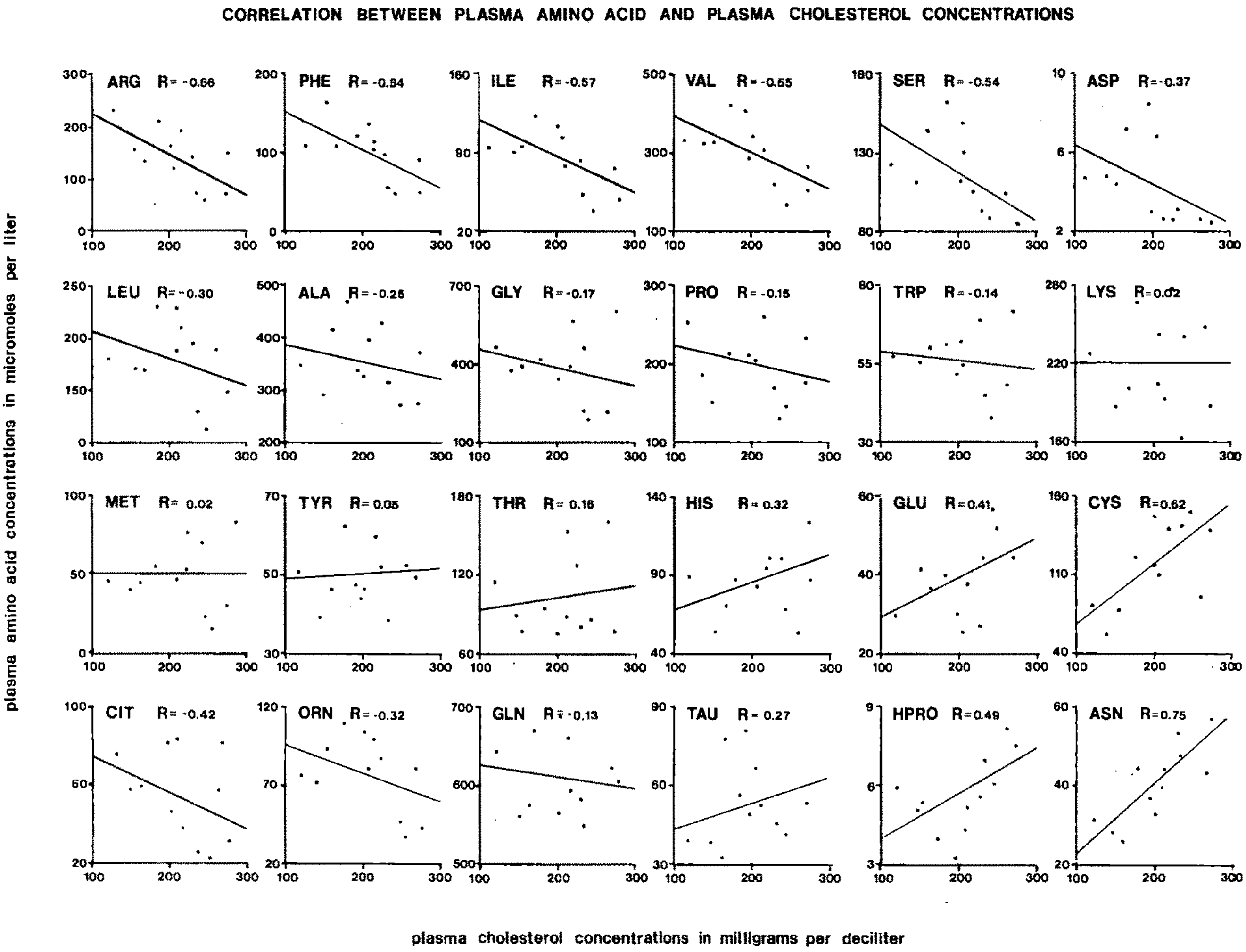

FIG. 25. Correlations between plasma amino acids and cholesterol levels in three patients during 90 days of Atheromine therapy. The first three rows represent the 18 amino acids in Atheromine and the bottom row represents metabolite amino acids.

occlusion of the left anterior descending, circumflex, and right coronary artery and the development of an extensive collateral network with a patent but stenotic vein graft to the right coronary artery and an ineffective left internal mammary graft. His ejection fraction, however, on his post-treatment examination had increased to 55%, representing a 92% improvement.

During and since his therapy he has had no further angina pectoris despite a greatly increased level of activity.

Figures 21–24 are graphic representations of the plasma concentrations of total cholesterol, LDL cholesterol, VLDL cholesterol, and HDL cholesterol during the 90-day period of the intravenous anticholesterol therapy in cases 2, 3, and 4.

Anticholesterol Solution Development

The anticholesterol therapy solution (Atheromine) consists of 18 L-amino acids formulated in quantities and ratios that are optimal for reducing plasma cholesterol concentrations in each patient. Starting with the base formula that evolved during the patient pilot study, modifications in the amino acid formulation are made depending on plasma and urine amino acid concentrations determined weekly until stable and then monthly thereafter. Figure 25 demonstrates the positive, negative, and neutral correlations between the individual plasma amino acids and plasma cholesterol concentrations derived from multiple determinations in three patients. Analyzing these data and plasma-to-urine ratios of the individual amino acids, the individual amino acids in the Atheromine can be adjusted to maximize its effectiveness in reducing plasma cholesterol concentrations.

Table 3 illustrates the average daily anticholesterol therapy solution that can be tailored to meet the nutritional needs of the patient while achieving maximum effectiveness in reducing plasma cholesterol concentration. Thus far, all patients have had the therapy on an ambulatory basis using a lightweight, portable, comput-

TABLE 3. *Average Daily Anticholesterol Therapy Solution*

Amino acids 10.31%	1000 mL
Isoleucine	4.0–10.0%
Leucine	5.0–10.0%
Lysine	4.5–6.5%
Methionine	3.5–5.5%
Phenylalanine	4.5–7.5%
Threonine	2.0–3.5%
Tryptophane	1.0–2.5%
Valine	4.0–9.0%
Alanine	7.0–16.0%
Arginine	9.0–18.0%
Histidine	1.5–3.5%
Proline	4.5–8.5%
Serine	2.5–6.5%
Tyrosine	0.0–1.0%
Glycine	3.0–8.0%
Glutamic Acid	3.5–5.5%
Aspartic Acid	2.0–4.0%
Cysteine	0.0–1.0%
Dextrose 20–50%	1000 mL
Calcium gluconate	4.7–9.4 mEq
Magnesium sulfate	30–36 mEq
Potassium chloride	0–60 mEq*
Potassium acetate	0–60 mEq*
Potassium phosphate	20–40 mEq*
Sodium chloride	40–80 mEq†
Sodium acetate	0–40 mEq†
Trace elements (MTE-5)	4 mL
Zinc sulfate	4.0 mg
Copper sulfate	1.6 mg
Manganese sulfate	0.4 mg
Chromium chloride	16 μg
Selenium	80 μg
Multivitamins (MVC 9 + 3)	10 mL
Vitamin A	3300 I.U.
Vitamin D	200 I.U.
Vitamin E	10 mg
Vitamin B1	3 mg
Vitamin B2	3.6 mg
Vitamin B3	40 mg
Vitamin B5	15 mg
Vitamin B6	4 mg
Vitamin B12	5 mg
Vitamin C	100 mg
Biotin	60 μg
Folic Acid	0.4 mg
Total water volume	2200 mL
Optional additives as indicated	
Vitamin K (Aqua-Mephyton)	
Folic Acid (Folvite)	
Iron Dextran (Imferon)	
Cimetidine (Tagamet)	
Insulin (Humulin)	
Heparin	
Zinc sulfate	
Copper sulfate	

* Total daily potassium dose = 80 mEq.
† Total daily sodium dose = 80 mEq.

erized pump (Pancretec, Inc., San Diego, CA) to guarantee desired infusion rates with maximum safety. No fat has been administered to the patients since the pilot study, and no evidence of biochemical or clinical fatty acid deficiency has been documented thus far. The cholesterol-reducing effects of the solution are greatly compromised by the oral intake of even minute amounts of lipid substrates and negated completely if the solution is infused by tube into the gastrointestinal tract in rabbits or in humans.

Discussion

Although atherosclerosis represents a spectrum of pathophysiology and clinical manifestations and although hypercholesterolemia represents only one of the causative or contributing factors to the development and progression of atherosclerosis, nonetheless a real and finite relationship between the two exists. Based on available epidemiologic studies, it is highly likely that the vast majority of atherosclerosis and its complications could be ameliorated, corrected, or avoided by strict adherence to an optimal diet providing only 100 mg of cholesterol, 20% of total calories as fat consisting of one-third saturated fat, one-third polyunsaturated fat, and one-third monounsaturated fat and a total caloric ration tailored to meet energy needs and maintenance of ideal body weight. However, it will be a major public health undertaking to convince Americans to make the radical changes in their current diets to achieve the optimal target diet outlined. Moreover, the changes in plasma cholesterol levels occur very slowly with oral dietary manipulation alone, and the hypercholesterolemic patient is usually discouraged within a few months of adhering to the diet because of the slow apparent progress. Moreover, it is difficult to achieve reductions of plasma cholesterol levels of greater than 8–10% by dietary manipulation alone.

The advantages of using a totally intravenous diet to stimulate reduction of plasma cholesterol levels are several: (1) the components of the diet can be finitely defined and precisely administered directly into the blood stream where they can immediately become involved in the appropriate biochemical reactions; (2) the cholesterol reduction effect of the optimal mixture of amino acids occurs rapidly to effect 40–60% reductions, which are unprecedented with any other single form of anticholesterol therapy; (3) the patient not only achieves prompt gratification and reward for the investment biochemically but also symptomatically as hyperlipidemia is reduced with corresponding decreased blood viscosity and increased microvascular perfusion; and (4) regression of atherosclerosis can be documented indirectly and/or directly by techniques that are currently rather crude but are destined to improve in simplicity, sophistication, and resolution.

This technique allows the application of clinical biochemistry directly to the management of a complex metabolic disorder with gratifying early biochemical and clinical results. The technique also allows a degree of control of the myriad biochemical processes of the body that is currently impossible to achieve with oral or enteral regimens. Thus the importance of any or all of the individual active components in the solution can be established finitely *via* direct intravenous infusion and without potentially detrimental modification by the digestive and absorptive processes of the alimentary tract. Eventually, however, the principles derived from the conscientious, meticulous study of the reactions and responses of patients with atherosclerosis to the intravenous nutrient mixtures herein described should allow the development of oral and enteral dietary formulations that will mimic or duplicate the biochemical milieu of the currently infused substrates after digestion, absorption, and assimilation. It is important that our efforts be directed toward achievement of these goals to allow the patient who has benefited from an intravenously induced hypocholesterolemia to maintain the accrued advantages after returning to a judicious oral diet after the intravenous therapy. The ultimate goal will be to prove the biochemical importance of maintaining much lower plasma cholesterol levels than we have accepted and tolerated as normal in the past not only to arrest and reverse atherosclerosis, but ultimately to prevent atherosclerosis. It is anticipated that this relatively pure biochemical approach to the management and control of the number one pathophysiologic process adversely affecting the health and longevity of our population will be rewarded with highly significant reductions in morbidity and mortality and greatly increase understanding of basic and clinical lipid and lipoprotein chemistry.

Acknowledgments

The contributions of the following co-workers to this project are gratefully acknowledged: Phillip R. Adams, Elizabeth R. Blume, Pamela R. Dieffenbach, Richard W. Drummond, DeAnn M. Englert, Andrew S. Feste, Stanley J. Gerlich, Mary Lou Gilliam, John T. Gordy, Edward J. Guinn, Carolyn M. Henry, Rhona J. Huntsman, Phillip E. Locey, Jun Maeda, Hugh A. McAllister, Theron C. Mock, Jr., Carolyn E. Moore, Judy C. Negele, Joseph J. O'Donnell, Charles Peters, Jacqueline Ruiz, Sheila M. Theiler, Betty W. Trotter, and Christann M. Vasquez.

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Discussion

DR. EDWARD M. COPELAND, III (Gainesville, Florida): The work that Dr. Dudrick has presented represents a culmination of 7 years of effort. I was privileged to see this project begin when I was still in Houston and have had the chance to follow its progress by various visits to Dr. Dudrick's laboratory.

I have had access to the manuscript and you, the audience, have not. To be able to give the amount of data contained in this manuscript in 10 minutes is impossible. I implore you to read the manuscript when it becomes available. It is excellent and represents a Herculean effort for which Dr. Dudrick and his colleagues should be congratulated.

Many questions arose while reading the paper. The solution does not work if given by gut. Dr. Dudrick might comment as to why. Will it work in the "garden variety" atherosclerotic patient as opposed to someone who has hereditary hyperlipidemia? Obviously, there are more people with "garden variety" atherosclerosis than with the other types of hyperlipidemia diseases. Does it work possibly in those patients with atherosclerosis but no hypercholesterolemia?

The published formula, called "Atheromine," is a range of concentrations for the individual amino acids, rather than a specific concentration for each amino acid. The concentration range was derived from multipe formula changes in both rabbits and patients to get a solution that would lower cholesterol maximally.

A further question, therefore, is: those of us who will use the solution, will we have to measure the serum and urine amino acids, as well as plasma cholesterol and various other lipids, to manipulate the concentration of the substrates to produce the data that you have, or will there be a single solution that we will be able to use much like that which evolved for the treatment of renal failure and hepatic failure?

DR. HENRY BUCHWALD (Minneapolis, Minnesota): I thank Dr. Dudrick for the privilege of reviewing this manuscript beforehand. I start with a few historic remarks: the ability of intravenous hyperalimentation solutions to depress lipid levels was first noted by Dr. Judah Folkman in 1972 in his work with total parenteral nutrition (TPN) solutions for glycogen storage disease. This work was confirmed by Dr. Starzl, our Program Chairman, and associates in 1973, in the use of TPN solutions as a preoperative test of potential efficacy before consideration of a portacaval shunt in patients with familial homozygous hyperlipoproteinemia. Again, this effect of TPN solutions was confirmed by Torsuch and Lees (1975), Stein and Meiny, and associates (1975), Cywes et al. (1976), and Yamashita and co-workers (1986). Most important, all of these studies showed that once you stopped infusion of TPN solutions, the hypolipidemic effect disappeared and the lipid levels returned to baseline.

I next turn to some of the items in Dr. Dudrick's paper and comment on them. I am a little confused about the atherosclerosis in the rabbits used in these experiments. Traditionally, if you give rabbits enough oral cholesterol, or enough of a dietary stimulus, to raise their cholesterol concentration over 1000 mg/dL, and then continue to follow these rabbits, they get progressive atherosclerotic disease, and it is ever progressive disease until they die. Thus, I question the validity of the visual inspection used by Dr. Dudrick of these lesions. Could his means of assessment not have been refined by use of scanning electronic microscopy, Folch analysis of vessel lipid content, or even simple dye staining to obtain a more accurate assessment of progression and regression? Finally, with respect to the animal data, I do not understand how he gets his numbers of 85% and 95%.

In terms of the clinical data, I was privileged to read in Dr. Dudrick's manuscript about four case studies. Dr. Dudrick, you had preoperative and postoperative arteriograms in all four patients, but in only one patient, the one you cited in your presentation, did you conclude that there was actual evidence of atherosclerotic regression on the arteriogram. Your data showed increases in flow rate, changes in symptoms, and alterations in Dopplers, but only one case showed, as I read the manuscript, a decrease in atherosclerosis.

The TPN solution advocated by Dr. Dudrick has three features that distinguishes it from the standard TPN solutions. There is a decrease in glycogen, a decrease in alanine, and an increase in arginine. Most interestingly, if the same solution is given orally, as has been noted by Dr. Copeland, the effect is negated. I cannot understand why.

I conclude from the data presented that this is an interesting pilot study. The work needs to be repeated in a randomized controlled trial in humans and it should not precede a commercialization at this point of a product.

I ask Dr. Dudrick several questions: what is the significance of these changes in these three basic amino acids? Why are glycine, alanine, and arginine altered so differently from their concentrations in other TPN solutions? With Dr. Copeland, I would like to ask, must this formula be individualized per patient or can a standard formula be developed, or can the blending of the formula be codified so that other investigators can do the same thing?

Again, I repeat the question why doesn't your solution work orally? Amino acids are absorbed without change from the intestinal tract; thus, why would this solution not work when administered orally?

Finally, what do you postulate is the biochemical mechanism by which your solution, in an isocaloric state, works to lower the serum lipids?

DR. HAROLD URSCHEL, JR. (Dallas, Texas): That was a fascinating presentation, and it could potentially mobilize the large cardiovascular labor force from bench work to more creative pursuits.

Previous search for the ideal "Draino" included our experiments with intra-arterial hydrogen peroxide in the late 1960s and early 1970s. It was based on the fact that hyperbaric oxygen reduced blood lipids and in some cases reversed atherosclerosis.

We must be careful in extrapolating the efficacy of any antiatherosclerotic drugs solely on the base of animal atherosclerosis, particularly hyperlipidemic rabbit atherosclerosis. With intra-arterial hydrogen peroxide, these lesions could be reversed in virtually 100% of animals completely. Even the induced hyperlipidemic lesions in primates consistently disappeared with intra-arterial hydrogen peroxide.

We tried this in over 100 patients with significant atherosclerotic obstructive lesions, and the results varied dramatically from total reversal to minimal regression or no effect.

A 95% stenosis in a unilateral vertebral artery not amenable to surgery in a patient with severe basilar artery insufficiency disappeared with 19 treatments of intra-arterial peroxide. The patient became asymptomatic for 4 years and died of carcinoma.

These data were presented to the Society of Vascular Surgery in 1975. It was totally ineffective in occluded arteries and in severely calcified arteries. These are similar limitations to angioplasty (PTCA) today.

I ask Dr. Dudrick what are the limitations of his technique. One of the arteries that we saw treated was totally obstructed (the right coronary artery). The rapidity that Dr. Dudrick showed the angiograms reminded me of Ken Cooper's speed of showing them when he was trying to demonstrate the effect of exercise on reversal of atherosclerosis. When you flash those angiograms past that quickly, it is difficult to assess the results.

We used hydrogen peroxide for cardiac resuscitation and treatment of acute myocardial infarction by retroperfusion of the coronary sinus, but discontinued its use because of the effective dose response was so close to the toxic effect on the enzyme system. I would like to know about the toxic effects in your dose-response curves and any deleterious side effects.

I think this is exciting, but caution should be employed until the clinical results are carefully assessed.

DR. ANTHONY M. IMPARATO (New York, New York): Dr. Dudrick is to be complimented on the exhaustive laboratory investigations that he has done with rabbits and the follow-up attempts to duplicate the results in humans. Carotid bifurcation plaques as seen in the operating room in both symptomatic and asymptomatic ischemic stroke patients vary considerably from patient to patient sharing in common mainly their localization at the carotid bulb and their content of fibrous tissue. They may be and probably are the prototype arterial lesions that cause ischemia in other parts of the body as well. Their evolution can be deduced, probably accurately, from observations in humans in the operating room and subsequent microscopic study.

May I lay the groundwork for two questions that I would like to ask by showing some slides?

(Slide) A carotid plaque appears to start as fibro-intimal thickening (Slide) which can be reproduced in the experimental animal by specific alterations of blood flow without alteration of diet. These are some of the models and these are the lesions at 1 year.

In humans it can progress to fibro-intimal plaque with intraplaque hemorrhage totally contained within the fibrous covering. (Slide) That is an early hemorrhage contained. (Slide) Gradual transformation of the hemorrhage to atheromatous debris can occur (Slide) until the so-called cholesterol abscess results. At any stage in the evolution of this plaque, thrombosis of the vessel can occur or embolization of a portion of the arterial wall producing ischemic stroke.

(Slide) This shows the portion of the arterial wall that is missing having embolized.

Would Dr. Dudrick speculate as to how lowering serum cholesterol in the human might influence this complex process of plaques' evolution? By what mechanism might ischemia be improved or relieved by lowering cholesterol?

DR. HIRAM C. POLK, JR. (Louisville, Kentucky): Dr. Dudrick, in response to specific inquiry from Council, you said that you would present objective evidence in humans of regression of atherosclerosis as well as describe the nature of the solution used. Would you specifically respond on both those counts, taking an extra minute to do so in your closing discussion?

DR. JOHN H. SIEGEL (Baltimore, Maryland): I congratulate Dr. Dudrick on opening up a whole new era on nutritional therapy, but I have some questions. It seems that a good deal of the response he has shown is due to a hypocaloric-controlled starvation in which he specifically reduced gluconeogenic amino acids and, therefore, to some extent also reduced lipogenic precursors.

I wonder if he could address the following questions. In both the experimental model and in humans, was the total caloric input in excess of metabolic needs, or was the caloric input negative with respect to the actual metabolic rate that these animals had?

Secondly, what effects did this nutritional program have on insulin secretion relative to the hypercaloric atherosclerotic diet where insulin is increased, since elevated insulin output in the control hypercaloric phase might cause increased synthesis of fatty acids? Was there a specific negative insulin secretory effect of the TPN solution used during the hypocaloric therapeutic period? Did those levels change?

Thirdly, is there any evidence of alteration in free fatty acid re-esterification before or after the therapeutic TPN period, since we did notice that when he restarted lipids he raised triglyceride levels severely. Does the TPN antiatheroslerosis diet therapy alter the tendency for re-esterification of administered lipids?

DR. GEORGE H. A. CLOWES, JR. (Boston, Massachusetts): Dr. Dudrick, before you come up, I would like to ask one question also. It seems to me that what you have shown us is that substitution of certain amino acids, perhaps for caloric value or for synthetic value, have had what looks like a beneficial effect.

I ask whether you have any data as to actually how these amino acids are used, studies with a radioactive tracer, or some other system?

DR. STANLEY J. DUDRICK (Closing discussion): My sincere thanks to all of the discussants. I greatly appreciate the comments and questions; each one is valid and appropriate.

This vital area is one of complex biochemistry. I do not believe that we can describe, explain, manage, or treat every manifestation or complication of atherosclerosis in the same way. As Dr. Imparato showed, there are various stages in the development of complex atherosclerotic lesions. There are also various causes, contributing factors, initiating factors, classifications, distributions, complications, etc. One must do the best one can in preventing and treating the usual presenting problems, and what cannot be managed adequately biochemically will require operative management.

Dr. Clowes, there is an enormous amount of work in the basic science literature showing positive correlations between the dietary intake of various sources of food and mortality rates secondary to coronary heart disease. In men between the ages of 55 and 59, animal protein had the highest positive correlation of 0.78 with a p value of less than 0.05, followed by cholesterol (0.76), meat (0.70), total fat (0.68), eggs (0.67), sugar (0.64), total calories (0.63), and animal fat (0.63). No correlation is demonstrable at $p < 0.05$ for plant sterols, fish, vegetable fat, or vegetables, and a negative or beneficial correlation exists for starch or complex carbohydrate (−0.46) and vegetable protein (−0.40).

The formulation of this solution resulted from a series of tedious, obsessive-compulsive laboratory experiments and observations. The solutions that were most effective in the rabbits and most effective in humans resembled plant or vegetable protein in their amino acid composition. Having started with intravenous amino acid mixtures with profiles derived from animal protein, which includes all kinds of meat, cheese, eggs, milk, even skim milk, we arrived at a mixture of amino acids that is similar to that of plant protein. Therefore, it appears that we have documented the wisdom of ingesting a vegetarian diet, which has been well described in the basic literature, and we have done it under the precise, well-controlled nutritional and metabolic conditions that can only be achieved intravenously.

Dr. Clowes, we have demonstrated reproducible correlations between plasma amino acids and plasma cholesterol concentrations in a series of meticulous studies in several atherosclerosis patients. Of the 18 component amino acids in the intravenous mixture, very strong inverse correlation between the plasma amino acid and the plasma cholesterol level was demonstrated for arginine, phenylalanine, isoleucine, valine, serine, aspartic acid, and leucine in decreasing order of importance and significance. The inverse correlations are not as significant for alanine, glycine, proline, or tryptophan. No correlation could be demonstrated between plasma cholesterol and plasma lysine levels, and there have been several published reports indicating that high arginine to lysine ratio has a positive correlation with lowering plasma cholesterol in animals.

Plasma methionine, tyrosine, and threonine show little or no correlation with plasma cholesterol levels, whereas histidine, glutamic acid, and cysteine show direct correlations between their plasma levels and plasma cholesterol level in increasing order of significance. Metabolite amino acids that are not in the mixture but appear in the plasma in significant amounts include citrulline, ornithine, glutamine, taurine, hydroxyproline, and asparagine. Strong inverse relationships exist for citrulline and ornithine, which are derivatives of arginine, the most important amino acid in the mixture. The inverse relationship for glutamine and cholesterol is less impressive, and the relationships between taurine, hydroxyproline, and asparagine are direct in increasing order of significance.

Dr. Buchwald, evidence for regression of atherosclerosis has been demonstrated clearly in three patients reported in this paper. There was not sufficient time in this 10-minute presentation to show all of the data included in the 25 figures in the paper.

Dr. Polk, the formula is presented with upper and lower limits for each component amino acid and compared with the currently available clinical intravenous amino acid mixtures. Starting at the median value for each amino acid, the mixture is individually formulated optimally for each patient based on plasma and urine amino acid and cholesterol levels. To date, this is the only manner in which the formula can be used clinically, but we are currently working toward an FDA approved formula suitable for mass production and distribution. The components of the mixture and the principles for their safe and effective formulation and use in patients are outlined in the paper. Your second question has been answered in my response to Dr. Buchwalds' query.

Dr. Copeland, when the amino acid mixture is administered *via* the alimentary tract in either rabbits or patients, the digestive processes destroy the effectiveness of the active ingredients in reducing plasma cholesterol or inducing regression of atherosclerosis. Therefore, we are currently engaged in studies to produce amino acid mixtures that when digested and absorbed, will mimic the milieu that we induce by direct central venous infusion.

I regret that there is insufficient time to discuss or answer the other comments and questions.

The Control of Diabetes Mellitus (NIDDM) in the Morbidly Obese with the Greenville Gastric Bypass

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Since February 1, 1980, the identical standardized Greenville Gastric Bypass has been performed in 397 morbidly obese patients with an operative mortality rate of 0.8%. The operation effectively controlled weight and maintained satisfactory weight loss even after 6 years (mean weights and ranges: Preoperative: 290 lbs (196–535); 18 months: 175 lbs (110–300); 72 months: 205 lbs (140–320). The gastric bypass favorably affected non-insulin-dependent diabetes (NIDDM), hypertension, physical and role functioning, and several measures of mental health. Rigorous follow-up (97.5% over 6 years) revealed that health problems were common in postoperative patients; there were nine late deaths. Abnormal glucose metabolism was present in 141 (36%) of 397 patients before surgery: NIDDM was present in 88 patients (22%) and 53 patients (14%) were glucose impaired. Of these, all but two became euglycemic within 4 months after surgery without any diabetic medication or special diets. The most recent 42 morbidly obese patients with NIDDM were studied intensively. In that cohort, fasting blood glucose, fasting insulin, and glycosylated hemoglobin returned to normal after surgery; insulin release, insulin resistance, and utilization of glucose improved sharply. The normalization of glucose metabolism after gastric bypass may not be related solely to weight loss and restriction of caloric intake, but may also be due to the bypass of the antrum and duodenum.

DIABETES MELLITUS is a frequent complication of morbid obesity. At least 25% of the morbidly obese have non-insulin-dependent diabetes mellitus (NIDDM) and an additional 10% demonstrate impaired glucose metabolism. This unusually high prevalence of diabetes may account for the high mortality of the morbidly obese from heart disease, atherosclerosis, and stroke.

From the Department of Surgery and the Division of Endocrinology, Department of Medicine, East Carolina University School of Medicine, Greenville, North Carolina

We have operated on 397 morbidly obese patients since February 1, 1980, and of these patients, 88 (22%) were afflicted with diabetes mellitus, whereas 53 (13%) demonstrated impaired glucose metabolism. A standardized gastric bypass operation was performed on all patients. Although we anticipated the diabetes mellitus of these morbidly obese patients would improve with their surgically induced weight loss, we were surprised by the rapidity of the improvement of glucose metabolism and the return to euglycemia even though the patients were still clearly morbidly obese and were still within 10–20 lbs of their preoperative weights. This report details our observations of the effect of the gastric bypass on diabetes mellitus. We also describe the effectiveness of the operation in controlling morbid obesity, reversing hypertension, and restoring functional effectiveness.

Methodology

From February 1, 1980 to February 1, 1987, we performed the identical standardized Greenville Gastric Bypass in 397 morbidly obese patients. The group included 343 women (86.4%) and 54 men (13.6%) of which 326 (82.1%) were white and 71 (17.9%) were black. The mean age was 37.6 years (range: 16–65).

Each patient was evaluated with a thorough medical assessment, an interview with a psychiatrist, and several instruments to measure mental health, physical and role functioning, economic status, and educational levels. Additional evaluations, including treadmill tests, cardiac catheterizations, endoscopies, and radiocontrast studies were done in some patients when indicated by the initial evaluation.

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Every morbidly obese patient without known diabetes mellitus had a 75-g oral glucose tolerance test (OGTT), as recommended by the National Diabetes Data Group[1] to determine whether they were truly nondiabetics. The 42 morbidly obese patients with diabetes who were recently operated on also had a 25-g intravenous glucose tolerance test to determine the rate of glucose disappearance (kg rate) and insulin concentrations before surgery. Of these 42 patients, 32 had the same tests 1 year after the gastric bypass surgery. Plasma glucose was measured by the Beckman-developed oxygen rate method.[2] Insulin was measured with the double-antibody method.[3] In addition, glycosylated hemoglobin was measured in these patients before and 1 year after surgery by affinity chromatography.[4,5]

All patients, whether referred by other providers or self-referred, were considered for initial evaluation. A patient was considered eligible for the surgery if: (1) he or she exceeded ideal body weight (as defined by the 1983 median weight of the Metropolitan Life Insurance Tables) by at least 100 lbs or if of short stature by 100%, (2) if the patient was an acceptable surgical risk, (3) if the patient was considered capable of understanding the operation and the postoperative consequences, and (4) if the patient gave informed consent.

Patients were usually admitted to the hospital on the day before surgery except for those in cardiorespiratory failure or those with other significant medical problems. Patients with such complications were often admitted several days before surgery to improve their surgical risk. Recently we have admitted a limited number of low-risk patients on the day of surgery, and these individuals have done well.

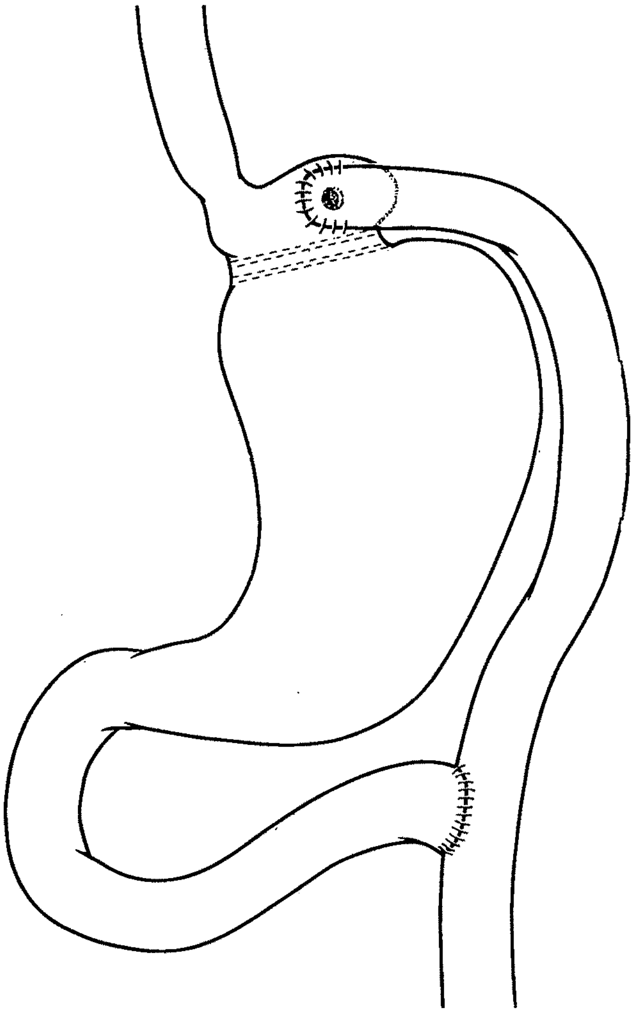

FIG. 1. The Greenville modification of the gastric bypass consists of 30-mL proximal gastric pouch joined to a 40-cm Roux-en-Y jejunal loop with a 0.8-mm gastroenterostomy.

The Greenville Gastric Bypass, a modification of the procedure devised by Mason,[6] has previously been described[7] in detail; a diagram of the procedure is shown in Figure 1. A Gomez retractor is useful. The abdomen is entered through a midline incision. If the exploration does not demonstrate contraindications to the procedure, specimens of blood, fat, liver, and muscle are taken for our basic science studies. Dissection around the upper portion of the stomach is begun by inserting the index finger gently into the angle at the cardia to the left of the esophagus. At this point there is a weak, thin area of the posterior peritoneum that is easily entered by the dissecting finger. The dissection is gently continued behind the esophagus and cardia and the finger brought out, not at the right side of the esophagus but between the ascending branches of the left gastric artery 2.5–3.0 cm below the esophagogastric junction. A large Malecot catheter (Division of Bard, Inc., Bard Urological Division, Murray Hill, NJ), from which the bulbous end has been cut, is used to pull a double-headed TA 90 Auto Suture stapling instrument (US Surgical Corp., Norwalk, CT) through the passage. A proximal pouch measuring 4 cm in width and 1.5 cm in height is then prepared by firing the staples. A figure-of-eight suture is placed at each end of the staple line to close the ends securely and to serve as guy sutures. The jejunum is divided at its apex, about 30–40 cm from the ligament of Treitz with the GIA stapling instrument and the distal end is then sutured to the gastric pouch. The anastomosis is sewn to fit snugly around a 0.8-cm Salem Sump tube (Sherwood Medical, St. Louis, MO) in two layers with continuous Prolene. The Roux-en-Y enteroenterostomy is then completed by joining the proximal jejunum end-to-side to the distal jejunum with GIA and TA 55 (US Surgical Corp.) stapling instrument. It is important to fasten the Roux loop to the mesocolon to prevent an internal hernia and to oversew any bleeders in the enteroenterostomy before closing it. The abdomen is closed with a running double-stranded 0 PDS absorbable suture. The skin is stapled. The operation can usually be performed in 60–75 minutes; blood loss rarely exceeds 300 mL.

TABLE 1. *Weight Loss after Gastric Bypass for the RY22 Cohort*

Time	N*	Mean Weight (lbs)	Mean % of Original Weight	Mean % of Ideal Body Weight
Before operation	397	290 (186–535)		212 (140–377)
1 month	251	261 (180–480)	90 (80–100)	191 (131–332)
6 months	323	207 (100–418)	72 (42–93)	152 (73–282)
12 months	240	184 (107–397)	63 (32–88)	134 (85–268)
18 months	172	175 (110–300)	61 (40–88)	120 (88–205)
24 months	160	176 (105–367)	61 (37–84)	130 (90–248)
36 months	120	187 (119–359)	64 (43–91)	138 (91–243)
48 months	99	188 (114–360)	65 (41–95)	139 (87–243)
60 months	57	195 (107–308)	69 (45–96)	144 (86–222)
72 months	26	205 (140–320)	72 (56–92)	149 (73–332)

* As of February 1, 1987.

Effect of the Gastric Bypass on RAND Mental Health Measures and Physical and Role Functioning

The effects of morbid obesity and the gastric bypass on mental health, physical and role functioning, *i.e.*, functional effectiveness were measured with the RAND instrument, the Obesity Awareness Scale (OAS), Eating Restraint Questionnaire (ERQ), Multidimensional Health Locus of Control (MHLC), the Zung Self-rated Depression Scale or SDS, and the Family Inventory of Resources for management (FIRM) before operation and during the course of follow-up in the most recent 120 patients.

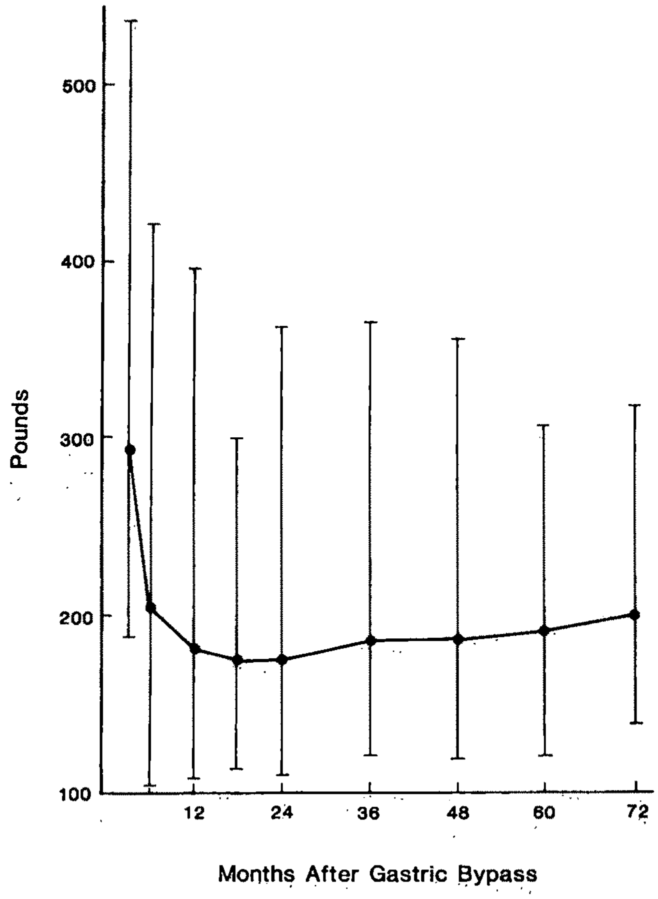

FIG. 2. Weight loss in pounds after gastric bypass in 397 morbidly obese patients.

Results

Follow-up

Follow-up has been rigorous. Of the 397 patients, only 10 did not keep long-term clinic appointments. Fortunately we have maintained contact with eight families of these 10 patients (97.5% follow-up).

Control of Weight

Weight reduction in these patients has been dramatic and well maintained over the 72 months of follow-up. Table 1 and Figure 2 present the weight loss of all 397 patients who have had the gastric bypass during the time intervals after surgery, in terms of mean weight in pounds, mean percentage of original weight, and mean percentage of ideal body weight. (Ideal body weight is determined from the midpoint of the "medium" standard of the Metropolitan Life Insurance Tables of 1983.)

If morbid obesity is defined as 100 lbs over ideal weight, 94% of the patients are "cured" within 2 years. There is, however, some weight gain between 24 and 72 months (176–205 lbs; 14%), reflecting a minority of individuals who learned to "outeat" their pouch and their dumping response by almost continuous snacking. These patients, *i.e.*, those who began to regain their weight, were the only ones given dietary limitations. Although we have had a few dietary failures, most patients will respond to the "Ensure Diet" (Ross Laboratories, Columbus, OH) (taking two cans of this supplement as the only caloric intake two or three times a week) or to formal dietary instruction by a trained dietician.

TABLE 2. *Effect of the Gastric Bypass on Diabetes*

	Before Operation	After Operation
Glucose Impaired	53	—
Diabetes Mellitus (NIDDM)	88	2
Receiving insulin	20	2
Receiving oral agents	13	1*

* One patient receives both insulin and an oral agent from her physician.

The Reversal of Diabetes Mellitus by the Gastric Bypass

The effect of the gastric bypass on adult onset diabetes mellitus (NIDDM) is the most significant finding of this study (Tables 2 and 3). Diabetes Mellitus (NIDDM) was present in 88 (22%) and impaired glucose tolerance was present in 53 (13%) of the 397 patients according to the criteria of the American Diabetes Association. All but two patients (99%) became and have remained euglycemic since surgery.

This normalization of glucose metabolism occurs with surprising speed. Frequently, patients became euglycemic within 10 days, even if they required over 100 units of insulin before surgery. The effect does not appear to be related solely to weight loss or decreased caloric intake, but may also be due to the bypass of the neuroendocrine axis of the antrum and duodenum.

The most recent 42 patients with diabetes were studied intensively. Of these, 12 had been receiving insulin, nine were receiving sulfonylureas, and another two were receiving both medications before the gastric bypass. Of these 42 patients, none now receive insulin and only one requires sulfonylureas. In all, fasting blood glucose, fasting insulin, and glycosylated hemoglobin were restored to normal levels. Insulin release, insulin resistance, and utilization of glucose were sharply improved. Although the maximum insulin release *per se* is not significantly different, these data should be considered in view of the preoperative and postoperative fasting insulin levels, *i.e.,* the basal values of 53 and 14 μU/mL. Thus the preoperative insulin release above basal was 23 μU/mL, whereas the postoperative response of the pancreas to the glucose load was 48 μU/mL, a significant improvement.

TABLE 3. *Effect of the Gastric Bypass on Measures of Glucose Metabolism*

	Before Operation (N = 42)	Year After Operation (N = 32)
Fasting blood glucose (mg%)	213 ± 15	117 ± 8
Fasting insulin (μU/mL)	53 ± 7	14 ± 1
Glycosylated hemoglobin (%)	12.3 ± 1.1	6.6 ± 0.6
Maximum insulin release (μU/mL)	76 ± 11	62 ± 15
Kg rate (%/min glucose disappearance)	0.65 ± 0.08	0.88 ± 0.07

TABLE 4. *Effect of the Gastric Bypass on Hypertension (N = 397)*

	Before Operation		After Operation	
	N	%	N	%
No. of hypertensive patients	225	56.7	73	18.4
Total no. receiving medication	144	36.3	53	13.3
Beta blocker	33	8.3	11	2.8
Diuretic	98	24.7	34	8.6
Vasodilator	11	2.8	6	1.5
Calcium blocker	2	0.5	2	0.5

The Control of Hypertension

Table 4 shows that of the 225 patients who were hypertensive (>140/90 mmHg) before surgery, only 73 remained so after the gastric bypass, a 68% decrease in the number of hypertensive patients. Similarly, the number of hypertensive patients requiring medication decreased from 144 to 53, a drop of 63%.

Effect of the Gastric Bypass on RAND Mental Health Measures and Physical and Role Functioning

The effects of morbid obesity and the gastric bypass on functional effectiveness were measured in our last 120 patients with the instruments listed under Methodology. These data will be reported separately, but in essence demonstrate that the operation sharply improves physical and role functioning, but that the mental health improvements noted during the first year may not be maintained.

Perioperative and Late Complications

The perioperative and late complications associated with this series of gastric bypass operations are summarized in Table 5.

TABLE 5. *Complications Associated With Gastric Bypass (N = 397)**

	N	%
Deaths		
Perioperative (2 Sepsis, 1 MI)	3	0.8
Late		
2 sepsis		
1 cancer of the larynx		
2 automobile accidents		
3 suicides		
1 cirrhosis	9	2.3
Complications		
All complications (major and minor)	390	98.2
Serious enough to delay discharge	45	11.3
Infections	70	17.6
Readmissions	124	31.2

* Mean length of stay = 8.7 days (range: 5–34 days).
MI = myocardial infarction.

TABLE 6. *Perioperative Complications, Within 30 Days after Gastric Bypass (N = 397)**

	N	%
Infections		
Minor wound infection	46	12.0
Severe wound infection	17	4.4
Subphrenic abscess	9	2.3
Intraperitoneal abscess	1	0.3
Postoperative temperature >103 F	16	4.2
Sepsis, unexplained	1	0.3
Peritonitis, otherwise unexplained	2	0.5
Technical problems		
Laceration of spleen	10	2.6
Laceration of liver	6	1.6
Staple misfire	5	1.3
Staple line bleed	2	0.5
Wound hematoma	4	1.0
Wound dehiscence	3	0.8
Wound seroma	28	7.3
Seroma with necrotic fat	12	3.1
Foreign body retained	1	0.3
Small bowel tear	1	0.3
Dehiscence with evisceration	1	0.3
Secondary wound closure needed	1	0.3
Enteric fistula	1	0.3
Systemic Problems		
Pneumonia	7	1.8
Pleural effusion	2	0.5
Arrhythmias	7	1.8
Congestive heart failure	1	0.3
Upper gastrointestinal bleed	2	0.5
Lower gastrointestinal bleed	1	0.3
Liver disease	2	0.5
Diabetic ketoacidosis	2	0.5
Summary		
Patients with complications	226	58.9
Deaths related to surgery	3	0.8
Reoperated	8	2.1
Readmitted	29	7.6

* As of February 1, 1987.

The perioperative mortality rate of 0.8% is low (3/397) for this group of high-risk patients with such complicating preoperative factors as Pickwickian syndrome, inadequately managed diabetes, cardiopulmonary failure, asthma, and disabling arthritis. The 30-day mortality rate (the usual way of defining perioperative mortality) is 0.5%, but since the third patient died on the 35th day of complications resulting from her operation, we have included her as a perioperative death in the summary Table 5. All of the perioperative complications occurring within the first 30 days after surgery are listed in Table 6.

Of the 397 patients who had surgery, 11% had a complication serious enough to prolong their hospital stay; 31.2% required readmission during the 6 years of follow-up for a problem directly or indirectly related to the obesity or the gastric bypass.

Patients who have gastric bypass operations require considerable postoperative medical support. During our 72 months of rigorous follow-up, 98% returned with a large variety of health problems; these are listed in Table 7. Although a number of these concerns were not directly related to the gastric bypass, many were. Problems such as depression, vitamin deficiencies, and dumping may be minor in terms of surgical statistics but are certainly major concerns for the patient and for those who bear the costs for the readmissions and extra office visits. Further, these complications may not become apparent for years, underscoring the great need for long-term follow-up of this and of other operations for morbid obesity.

TABLE 7. *Late Complications and Other Complaints Recorded During the Follow-up of Gastric Bypass Patients More Than 30 Days after Surgery (N = 397)**

	N	%
Infections		
Wound infections/stitch granuloma	8	2.1
Wound necrotic fat	7	1.9
Severe wound infection	4	1.1
Technical problems		
Loose suture in anastomosis	8	2.1
Anastomotic failure by endoscopy (dilated)	9	2.4
Incisional hernia	56	15.0
Dilted proximal pouch	13	3.5
Gastritis by endoscopy	47	12.6
Marginal ulcer	8	2.1
Stenosis of anastomosis; Rx: dilatation	6	1.6
Small bowel obstruction	19	5.1
Systemic problems		
Skin lesions	22	5.9
Musculoskeletal complaints	34	9.1
Headache, neurovisual symptoms	147	39.3
Chest pain	31	8.3
Renal stones	8	2.1
Constipation	151	40.4
Temporary hair loss	124	33.2
Hemorrhoids/fissure	15	4.0
Arthritis	12	3.2
Vitamin B12 deficiency	101	27.0
Other vitamin deficiencies	40	10.7
Dairy food intolerance	178	47.6
Bile reflux/esophagitis	14	3.7
Genitourinary complaints	11	2.9
Hypoglycemia	13	3.5
Psychiatric problems/stress	27	7.2
Depression/Rx: medication	5	1.3
Depression/Rx: psychotherapy	68	18.2
Depression/Rx: hospital	6	1.6
Pedal edema	22	5.9
Colitis	4	1.1
Arrhythmias	48	12.8
Urinary tract infection	33	8.8
Cholelithiasis	27	7.2
Dumping	265	70.9
Nausea/vomiting	58	15.5
Diarrhea	57	15.2
Anemia	55	14.7
Dehydration/malnutrition	15	4.0
Peripheral neuropathy	7	1.9
Abdominal pain	63	16.8
Summary		
Deaths related to surgery	1	0.3
Late deaths unrelated to surgery	8	2.0
Patients with late complications	364	97.3
Readmissions	93	24.9

* As of February 1, 1987.

Most disturbing are the nine late deaths, a late mortality rate of 2.3% (9/397). Although no deaths seem to be directly related to the surgery, they raise concerns. The two deaths from automobile accidents, the three suicides, and the one death from cirrhosis suggest that the gastric bypass does not alleviate the depression commonly seen in the morbidly obese; in fact, the dramatic change in body image and forced modification of eating behavior may exacerbate it in a few patients. Similarly, the two deaths from sepsis and the death from cancer of the larynx raise questions about the effect of the induced malnutrition on immunocompetence in these patients. A tenth late death is expected soon: a woman dying of AIDS, probably acquired from a blood transfusion given during a plastic surgical procedure over a year after her gastric bypass. This mortality will raise the late death rate to 2.5% Unfortunately, we do not have reliable comparison figures for the illness or mortality rate of morbidly obese individuals who did not have surgery.

Discussion

NIDDM or Type II diabetes mellitus represents approximately 85% of all patients with diabetes. It is a heterogeneous disorder characterized by defects in insulin action and insulin secretion.[8–12]

When NIDDM is associated with obesity, insulin resistance significantly worsens. Over 75% of patients with NIDDM are obese and those who are morbidly obese (defined as at least 100 lbs or more than 100% over their ideal body weight) are most frequently refractory to insulin or sulfonylurea therapy, dietary counseling, or physical therapy.

Weight reduction clearly improves NIDDM and dietary control remains the hallmark of treatment for this disease. Consequently, dieting has always been a mainstay in the clinical management of NIDDM. Although the amelioration of NIDDM after jejunoileal bypass had been recognized for a long time, Ackerman[13] was apparently the first to note the rapidity (in days) with which objective improvements in carbohydrate metabolism occurred. Previously the improvement associated with intestinal bypass was considered to be a direct result of massive weight loss, but Ackerman speculated that the early return to glucose tolerance, even during the period of perioperative stress, must have a more complex explanation. He considered such possibilities as decreased carbohydrate ingestion, glucose malabsorption, and the diminution in measured gastric inhibitory polypeptide (GIP) and its insulinotropic effect after intestinal bypass. Halverson et al.[14] have reported similar findings after gastric bypass. They described alterations in glucose tolerance, insulin response, and insulin sensitivity 20 months after surgery. Excess weight loss was accompanied by improvements in insulin receptor number, basal hyperinsulinemia, and glucose tolerance. They also described an unexpected rise in GIP and insulin after the ingestion of oral rather than intravenous glucose in patients after operation, perhaps accounting for the episodic hypoglycemia sometimes seen in these individuals after gastric bypass. Herbst et al.[15] confirmed similar findings in morbidly obese diabetics who had gastric restriction operations and credited the improvement to increased insulin receptors. Schrumpf et al.[16] also reported the positive effect of the gastric bypass on glucose tolerance in obesity and credited this change to lowered basal insulin secretion and increased hepatic extraction of insulin.

Our population of morbidly obese patients with NIDDM has the same characteristics as other similar populations previously described.[14,15,17–19] These patients have fasting hyperinsulinemia, fasting hyperglycemia, and a decreased glucose disappearance rate currently attributed to overall insulin resistance, increased glucose production by the liver, and reduced peripheral glucose utilization. The increment of insulin secretion by the pancreas during the first 10 minutes after the administration of 25 g of glucose intravenously is severely decreased, characteristic of the abnormal first phase of insulin release seen in patients with NIDDM. Furthermore, the glycosylated hemoglobin is increased, indicative of long-term hyperglycemia.

The mechanism of insulin resistance in these severely obese patients with NIDDM currently is unknown. We have developed methodologies to study the three major target organs of insulin action in humans: the liver, muscle, and adipose tissue.[20–23] We have found that the insulin receptor kinase is greatly decreased, compared with controls, in liver and adipose tissue, but not in skeletal muscle. Since the insulin receptor kinase might be involved in the intracellular message of insulin action, our studies so far have provided the first demonstration of a functional abnormality of the insulin receptor in NIDDM. In the muscle, the defect in insulin action might be distal to the insulin receptor kinase.

After gastric bypass surgery there is a dramatic improvement in overall carbohydrate metabolism, insulin action, and insulin secretion in the absence of pharmacologic therapy. From the clinical point of view, the most important observation is that the patients can maintain normal glycosylated hemoglobin. However, it should be recognized that if they are challenged with 25 g of glucose intravenously, it is clear that the ability of the pancreas to secrete insulin and the peripheral tissues to utilize glucose, although greatly improved, is not normal. However, under physiologic conditions, rarely, if ever, do these patients encounter a 25-g glucose load in blood within 1 minute.

The mechanism of improvement of NIDDM after gastric bypass is, no doubt, complex and due to a num-

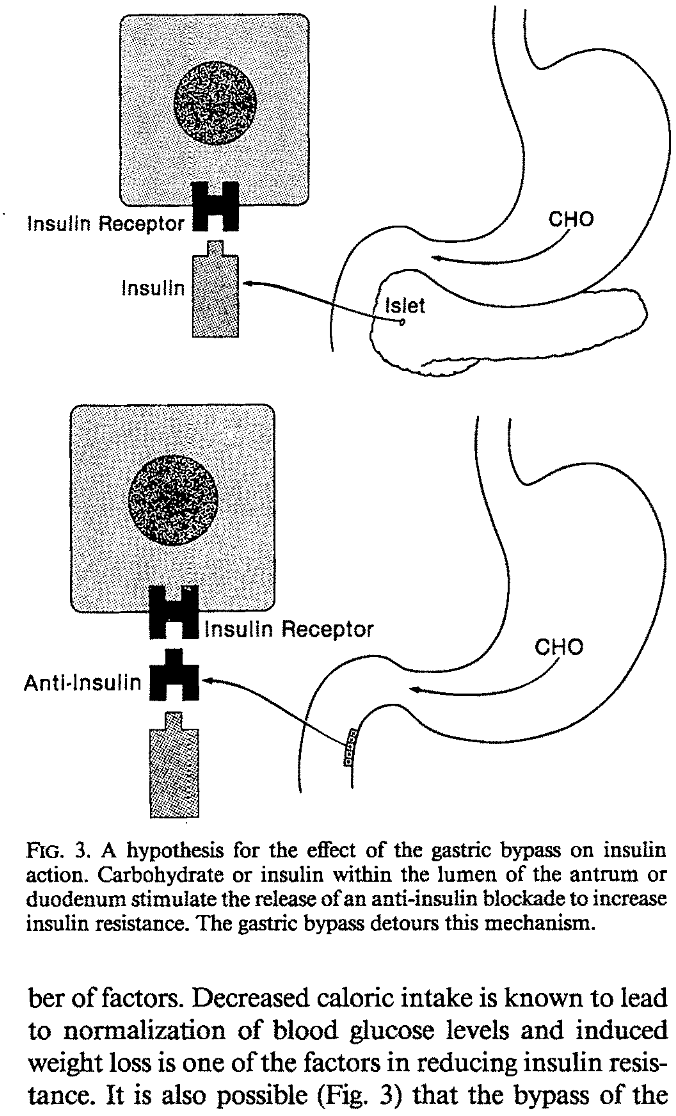

FIG. 3. A hypothesis for the effect of the gastric bypass on insulin action. Carbohydrate or insulin within the lumen of the antrum or duodenum stimulate the release of an anti-insulin blockade to increase insulin resistance. The gastric bypass detours this mechanism.

ber of factors. Decreased caloric intake is known to lead to normalization of blood glucose levels and induced weight loss is one of the factors in reducing insulin resistance. It is also possible (Fig. 3) that the bypass of the antrum and duodenum decreases the stimulation of endocrine cells to produce an anti-insulin blocking agent that influences the action of GIP. Most biologic systems have "stop and go" controlling systems; it is reasonable to expect that there is also an anti-insulin mechanism that responds either to high levels of glucose or insulin within the upper gut. We plan to explore this thesis with a prospective randomized comparison between the effect of the gastric bypass (which bypasses the antrum and duodenum) and the vertical banded gastroplasty (which does not) in a series of morbidly obese patients with NIDDM.

In summary, our series demonstrates that the Greenville version of the gastric bypass is an effective therapy for morbid obesity. The operation produces predictable control of weight, controls NIDDM in almost all patients, ameliorates most cases of hypertension, and sharply improves the functional effectiveness and quality of life in the morbidly obese. The operation is generally well tolerated and can be performed with a low mortality, but the patients must be followed closely for years because malnutrition, late complications of surgery, and psychiatric problems are not uncommon.

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Discussion

DR. EDWARD E. MASON (Iowa City, Iowa): Thank you, Dr. Pories for calling attention to this effect general surgeons have on the ratio of benefit to risk in treating extreme obesity with stomach reduction surgery.

The effect is not peculiar to gastric bypass. (Slide) Vertical banded gastroplasty produces the same severe reduction in insulin requirement with the cost savings as much as $4000 in 5 years by elimination of the need for 100 units of insulin per day.

(Slide) What is happening? Vertical banded gastroplasty does not rearrange the gastrointestinal tract, which means that there is no deleterious effect on the absorption of iron, calcium, and certain vitamins, and probably no change in the release of digestive tract hormones.

(Slide) The benefit of all gastric reduction operations is dependent on careful measurement of pouch volume and the outlet, and over the long term of doing something to reinforce the outlet (Slide) to make sure it will not dilate.

(Slide) Vertical banded gastroplasty causes the same severe reduction in weight and usually the elimination of need for insulin, and in this and other ways is as effective as less physiologic operations that rearrange the digestive tract.

(Slide) Why does the insulin requirement drop from 100 to zero so rapidly? Before the patient is released from the hospital, the preoperative insulin level decreases from as high as 100 or 120, often to zero. This occurs probably because of the very severe reduction in glucose intake.

We know, however, according to Dr. Pories' presentation, that there was a doubling in the rate of glucose utilization. When does this occur? Does it occur in the first few days when the requirement for insulin drops? And, in those occasional patients who disrupt the operation or learn to overeat the restriction and regain weight, how long does it take for the cells to lose their insulin receptors?

We have an opportunity here to learn more about the mechanisms of the benefits we produce, and I look forward to hearing more about the mechanisms involved.

DR. EDWARD R. WOODWARD (Gainesville, Florida): We also have observed excellent weight loss after Roux-en-Y gastric bypass and early reversal of diabetes mellitus in nearly all cases. We have operated on 412 patients since 1982 using this procedure. A 2-year follow-up of 238 patients has revealed an average loss of excess weight of 66%. Three-year follow-up of 150 patients has revealed an average loss of excess weight of 64%. We have been particularly pleased with the 4-year follow-up in 67 patients where the average loss of excess weight has been 76%.

We have observed a higher incidence of marginal ulceration than that noted in this report. This diagnosis has been established in 30 of our patients, an incidence of 7%. Eighteen of these were refractory to medical therapy and required reoperation. It is interesting that in 17 of the 30 patients, a defect in the staple line had developed and most of the medically intractable patients were in this group. It appears the staple line defect permitted reflux of acid gastric juice from the main stomach.

In the last 2 years we have had considerable experience using a vertically stapled gastric partition with a Silastic® band controlling the pouch outlet. This is the method described by Dr. Henry Laws of Birmingham (Am J Surg 1981; 141:393–394.). We have noted the same early reversal of diabetes mellitus in these patients, indicating the likelihood that drastically reduced calorie intake is a major factor.

DR. BERNARD M. JAFFE (Brooklyn, New York): I, too, was privileged to review the manuscript. Dr. Pories asked if I would spend a moment speculating as to the possible mechanisms that resulted in improvement of insulin function.

One of the possibilities must be related to dietary changes. However, the documentation that glucose tolerance tests and euglycemic and hyperglycemic clamps resolve so rapidly after operation suggests that it is simply not a matter of dietary glucose or dietary carbohydrate.

Another possible mechanism includes an abnormality in gastrointestinal hormones, and in response to Dr. Pories' request, I have thought about some possible humoral mechanisms that could be involved.

Pancreatic polypeptide is known to be involved in the control of insulin release, and levels of PP are profoundly suppressed in obesity. On the other hand, despite these two pertinent observations, PP is unlikely to be the mediator of this phenomenon. Reversal of the abnormality in PP requires restoration of normal weight, *i.e.*, a much slower effect than that observed in these clinical experiments. Therefore, PP is not the agent.

Somatostatin is another possibility, and obviously bypassing of the antrum would result in lessening of the release of somatostatin. To date, nobody has been able to successfully document changes in physiologic circulating somatostatin levels. The best evidence that makes it unlikely that somatostatin participates in the response is the fact that both the banded gastroplasty and the Roux-Y gastric bypass provide exactly the same alteration, the rapid resolution of the diabetic phenomenon. Since somatostatin is abnormally released in one circumstance and not in the other, antral exclusion certainly does not yield the mechanism.

I believe the phenomenon is probably a matter of resolution of the abnormal insulin resistance. As a result of the correction of insulin resistance, which has been shown to occur rapidly, basal levels of insulin return to normal, and insulin no longer participates in vicious negative feedback inhibition. As a result of these changes, insulin responsiveness returns to normal.

I believe the key phenomenon is the change in insulin resistance, and when we understand why this occurs, I believe we will understand more about this phenomenon.

DR. LEON MORGENSTERN (Los Angeles, California): Dr. Pories, I would like to ask if there were any accidental splenectomies in this large series, and if so, was there any relation to early or late sepsis?

DR. WALTER J. PORIES (Closing discussion): First I would like to thank each of the discussants and, obviously, thank Dr. Mason for having the idea in the first place.

We agree that a comparison between the gastric bypass and the vertical banded gastroplasty offers the elegant experiment to test the effect of the antral and duodenal hormones on glucose metabolism, especially if insulin function and resistance are measured with the rigorous methodology of the insulin clamp. Accordingly, we plan to perform this prospective comparison in the near future and will begin as soon as we have the approval from our institutional review board.

Dr. Woodward, I cannot explain why your number of marginal ulcers is higher than ours (8/397; 2.1%). The use of cimetidine has made it possible to manage these without surgery; we believe that this is a major breakthrough.

I stand in awe of Dr. Jaffe and I have for some time. His speculations are exciting and I hope that he will share his ideas with us during the planning of our next studies.

As Dr. Morgenstern guessed, we have had splenic injuries. There have been 10 (2.6%) in this series and most of these occurred during the first 2 years. Increased experience has helped to diminish this complication.

Comparison of Whole Pancreas and Pancreatic Islet Transplantation in Controlling Nephropathy and Metabolic Disorders of Diabetes

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To compare the long-term effectiveness of whole pancreas transplantation and pancreatic islet transplantation in controlling the metabolic disorders and preventing the kidney lesions of alloxan diabetes, metabolic and morphologic studies were performed in four groups of rats: (1) NC-116 nondiabetic controls; (2) DC-273 untreated alloxan-diabetic controls; (3) PDT-182 rats that received syngeneic pancreaticoduodenal transplants not long after induction of diabetes with alloxan; and (4) IT-92 rats that received an intraportal injection of at least 1500 and usually 2000 syngeneic pancreatic islets soon after induction of diabetes with alloxan. Each month for 24 months after diabetes was well established, body weight and plasma concentrations of glucose and insulin were measured, and five lesions were scored by light microscopy in 50 glomeruli and related tubules in each kidney by a "blind" protocol: glomerular basement membrane thickening, mesangial enlargement, Bowman's capsule thickening, Armanni-Ebstein lesions of the tubules, and tubular protein casts. There were progressive and highly significant increases in the incidence and severity of all five kidney lesions in the diabetic control rats compared with the nondiabetic control rats. No significant differences were found between the kidneys of Group PDT and those of Group NC, demonstrating that whole pancreas transplantation prevented all of the diabetic kidney lesions throughout the 2-year study period. In contrast, within 3–9 months after pancreatic islet transplantation and thereafter, the incidence and severity of the five diabetic kidney lesions were similar in Group IT and Group DC. Whole pancreas transplantation produced precise metabolic control of diabetes throughout the 24 months of study, whereas pancreatic islet transplantation did not accomplish complete metabolic control, particularly beyond the first several months after transplantation. The difference in the completeness of metabolic control achieved by the two types of transplants is the most likely explanation for their sharp difference in effectiveness in preventing diabetic nephropathy.

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MANY RECENT STUDIES have established that insulin-dependent diabetes mellitus (IDDM) is caused by destruction of the beta cells of the pancreatic islets in a genetically susceptible subject.[1-7] Considerable evidence suggests that the metabolic disorders resulting from loss of beta cells in IDDM are the underlying cause of the progressive secondary complications that develop in the kidney, eye, nervous system, and vasculature. Standard therapy of IDDM with insulin injections and diet has not prevented these secondary complications, presumably because of failure to precisely control the metabolic disturbances.[8-10] Consequently, there is great interest in various types of endocrine pancreas replacement therapy, based on the hope that such treatment will restore physiologic beta cell function and strict metabolic control. However, it is not yet known if any form of endocrine pancreas replacement therapy is capable of preventing, stabilizing, or reversing the lesions of IDDM.

Diabetic kidney disease is the most common cause of death in IDDM, and currently is the most frequent diagnosis in patients who have kidney transplantation or chronic hemodialysis in the United States.[11] Rats with diabetes mellitus (DM) induced by chemical agents that destroy the beta cells of the islets of Langerhans, such as alloxan and streptozotocin, develop renal lesions that appear similar to those found in patients with IDDM, particularly glomerular capillary basement membrane thickening and mesangial enlargement.[12-20] The alloxan diabetic rat, therefore, is a suitable animal model in which to evaluate the effectiveness of therapy on diabetic nephropathy.

Currently, three forms of endocrine pancreas replacement therapy are undergoing intensive investigation: (1) artificial insulin delivery devices; (2) transplantation of

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islets of Langerhans; and (3) transplantation of the whole pancreas or a segment of the pancreas as a vascularized graft. Artificial insulin delivery devices have not arrested the progression of or reversed diabetic nephropathy, retinopathy, or neuropathy in the few clinical studies that have been reported to date, perhaps because these devices do not achieve strict metabolic control.[21-32] There have been no studies in humans of the long-term effectiveness of either pancreatic islet transplants or whole pancreas transplants in controlling the metabolic disorders and secondary complications of IDDM, and few studies in animals. Moreover, no studies have been performed comparing the effects on any aspect of diabetes of islet transplants and whole pancreas transplants. Therefore, the current investigation was done to compare, in the same research laboratory, the long-term effectiveness of the two types of pancreas transplantation in providing strict metabolic control and preventing kidney lesions in highly inbred rats with alloxan diabetes over 2 years.

Methods

Experimental Groups

Six-month-old, highly inbred Lewis strain rats (Simonsen Laboratories, Gilroy, CA), which uniformly accept tissue transplants from each other without rejection, were housed two to five to a cage and fed standard rat chow and water *ad libitum* throughout the study. The animals were distributed among four groups as follows: (1) *Group NC* (nondiabetic control) contained 116 unaltered rats. (2) *Group DC* (diabetic control) contained 273 untreated diabetic rats in which DM was induced by intravenous injection of alloxan monohydrate (Sigma Chemical Co., St. Louis, MO) in a dose of 42–44 mg/kg. For acceptance into the study, rats were required to have plasma glucose levels that were above 200 mg/dL on both the third and seventh days after alloxan injection. Most rats had plasma glucose levels above 300 mg/dL. (3) *Group PDT* (pancreaticoduodenal transplant) contained 182 rats that received a heterotopic pancreaticoduodenal isograft from an age-matched donor rat 1 week after DM was established by the same method used in Group DC. (4) *Group IT* (islet transplant) contained 92 rats that received 1500–2000 syngeneic pancreatic islets from age-matched donor rats by injection into the portal vein 1 week after DM was established by the same method used in Group DC.

Every month for 24 months after onset of DM, two to four rats from each group were killed for quantitative morphologic studies of kidney pathology. Since the measurements of kidney lesions spanned from age 7 months to age 30 months, and the normal life span of the Lewis rat in our laboratory usually ranges from 24–30 months, the studies of diabetic nephropathy extended over nearly the entire life span of the rats.

Technique of Whole Pancreas Transplantation

In 1971, we devised the microvascular surgical technique of heterotopic pancreaticoduodenal transplantation in the rat.[33,34] The pancreaticoduodenal graft was harvested from the donor rat with a segment of aorta containing the celiac and superior mesenteric arteries supplying the graft, and with a segment of portal vein containing the venous drainage from the graft. The pancreaticoduodenal graft was transplanted into the recipient rat by performing end-to-side vascular anastomoses with continuous 9-0 nylon sutures between the graft aortic segment and the host aorta, and between the graft portal vein segment and the host inferior vena cava. The proximal end of the graft duodenum was closed and the distal end was anastomosed to the side of the third portion of the host duodenum using a continuous 7-0 silk suture. Graft ischemia time was 25 ± 5 minutes.

Technique of Pancreatic Islet Transplantation

Pancreatic islets were obtained from 10–12 donor rats by the collagenase digestion method of Lacy and Kostianovsky.[35] The common bile duct was perfused with Hanks solution to distend the pancreas and disrupt the acinar tissue, and the pancreas was removed and minced into fine fragments with scissors. The pancreatic fragments were digested with collagenase (Sigma Type V, Sigma Chemical Co., St. Louis, MO) in a shaker water bath and serially washed and centrifuged. The islets were separated from remaining acinar tissue by Ficoll gradient centrifugation, which was followed by serial washing and centrifugation. The number of islets in an aliquot of the pool was counted under a microscope. The pool of fresh islets was placed in a syringe and injected immediately into the portal vein of a diabetic recipient rat through a 25-gauge needle. Each recipient received an intraportal injection of at least 1500 islets, but the vast majority of recipients were given approximately 2000 islets.

Metabolic Studies

All rats had metabolic studies done. Monthly measurements were made of body weight and plasma concentrations of glucose and insulin. Intraperitoneal glucose tolerance tests were done monthly. Plasma glucose was measured by a modification of the O-toluidine method and plasma insulin was measured by a specific double antibody radioimmunoassay. All blood specimens were obtained from the rats' tail vein between 9:00 A.M. and 10:00 A.M., and the animals were not fasted.

TABLE 1. *Mean Body Weight (g) ± SEM at Intervals for 24 Months in Four Groups of Rats*

Group	First Day of Study		1 Month		3 Months		6 Months		9 Months		12 Months		15 Months		18 Months		21 Months		24 Months	
	N	Mean ± SEM	N	Mean ± SEM	N	Mean ± SEM	N	Mean ± SEM	N	Mean ± SEM	N	Mean ± SEM	N	Mean ± SEM	N	Mean ± SEM	N	Mean ± SEM	N	Mean ± SEM
NC	116	337 ± 2.5	116	399 ± 2.2	116	445 ± 2.9	103	487 ± 3.2	95	509 ± 3.3	109	536 ± 3.9	97	558 ± 5.4	82	548 ± 6.5	60	538 ± 8.8	47	517 ± 12.4
DC	273	327 ± 2.1	273	323 ± 2.7*	206	326 ± 3.3*	209	327 ± 3.6*	156	318 ± 4.4*	124	324 ± 4.5*	101	333 ± 5.6*	53	332 ± 7.3*	20	341 ± 9.1*	17	330 ± 15.3*
PDT	182	328 ± 2.6	182	386 ± 2.8	161	435 ± 2.8	136	467 ± 3.4	127	484 ± 4.1	104	488 ± 5.1	84	489 ± 6.0*	47	480 ± 8.0*	24	467 ± 13.9*	10	433 ± 29.5*
IT	92	326 ± 2.9	92	384 ± 3.5	58	436 ± 5.7	55	447 ± 5.8*	35	462 ± 8.7*	27	453 ± 10.6*	22	465 ± 20.1*	19	443 ± 16.8*	4	367 ± 25.9*	3	339 ± 15.8*

* Significantly lower than NC ($p < 0.001$).
NC = nondiabetic control rats.
DC = untreated diabetic control rats.
PDT = diabetic rats that received a syngeneic pancreaticoduodenal transplant.
IT = diabetic rats that received a syngeneic pancreatic islet transplant.

The detailed results of the metabolic studies will be the subject of a separate report.

Morphologic Studies of Kidney Lesions

Kidney tissue obtained at autopsy each month for 24 months was fixed in 10% buffered formalin, embedded in paraffin, cut into sections 4-μ thick, and stained with hematoxylin and eosin, Mallory's trichrome, and periodic acid-Schiff stains. The sections were coded to mask their identification by the examiner and eliminate observer bias, and the code was not broken until the study was completed. Fifty glomeruli and the related tubules from each kidney were examined by light microscopy without knowledge of the group from which the tissue had been obtained, and the following five lesions were scored on a scale of 0 (absent), 1 (mild), 2 (moderate), and 3 (severe): glomerular basement membrane thickening (GBMT), mesangial enlargement (ME), Bowman's capsule thickening (BCT), Armanni-Ebstein lesions of the tubules (A-E), and tubular protein casts (PRO). The scores for each lesion were expressed as a total count per rat by adding the individual scores for each glomerulus and related tubules. Morphologic studies of kidney lesions were performed in 63 rats in Group NC, 104 rats in Group DC, 91 rats in Group PDT, and 92 rats in Group IT.

Statistical Analysis

A two-tailed Student's t-test was used to examine differences between mean values.

Results

Metabolic Studies

Table 1 shows the results of serial measurements of body weight. Untreated diabetic control rats (Group DC) did not gain weight throughout the 2-year study period. Pancreaticoduodenal transplants were significantly more effective than pancreatic islet transplants in stimulating weight gain and growth in diabetic rats ($p < 0.001$ from the 6th to the 24th months between Group PDT and Group IT). After the 20th month, mean body weights in Group IT and Group DC were not significantly different.

Table 2 shows the mean plasma glucose levels in the four groups of rats. The untreated diabetic control rats (Group DC) had plasma glucose levels that were three times those found in the nondiabetic controls (Group NC) ($p < 0.001$). Pancreaticoduodenal transplantation (Group PDT) reduced the diabetic plasma glucose levels to normal and maintained strict metabolic control throughout life. Mean plasma glucose concentrations in the rats with whole pancreas transplants were not signifi-

TABLE 2. *Mean Plasma Glucose (mg/dL) ± SEM at Intervals for 24 Months in Four Groups of Rats*

	First Day of Study		1–3 Months		4–6 Months		7–9 Months		10–12 Months		13–15 Months		16–18 Months		19–21 Months		22–24 Months	
Group	N	Mean ± SEM	N	Mean ± SEM	N	Mean ± SEM	N	Mean ± SEM	N	Mean ± SEM	N	Mean ± SEM	N	Mean ± SEM	N	Mean ± SEM	N	Mean ± SEM
NC	116	92 ± 1.1	116	87 ± 1.6	105	117 ± 2.2	98	87 ± 1.1	113	82 ± 1.3	106	85 ± 1.3	91	83 ± 1.1	76	85 ± 1.2	42	98 ± 1.6
DC	273	402 ± 7.2*	272	288 ± 6.0*	245	305 ± 5.9*	198	297 ± 4.6*	156	303 ± 5.1*	134	296 ± 5.3*	84	270 ± 8.6*	43	299 ± 14.9*	28	264 ± 6.3*
PDT	182	385 ± 6.9*	171	86 ± 1.1	154	92 ± 1.6	129	89 ± 1.3	106	89 ± 1.3	81	89 ± 2.4	41	89 ± 2.6	12	105 ± 12.3	9	92 ± 6.0
IT	92	348 ± 6.8*	92	116 ± 2.2*	87	138 ± 4.5*	87	158 ± 7.2*	79	155 ± 6.4*	41	154 ± 8.7*	28	150 ± 10.6*	4	143 ± 18.7*	3	143 ± 3.8*

* Significantly higher than NC ($p < 0.001$).
NC = nondiabetic control rats.
DC = untreated diabetic control rats.
PDT = diabetic rats that received a syngeneic pancreaticoduodenal transplant.
IT = diabetic rats that received a syngeneic pancreatic islet transplant.

TABLE 3. *Mean Plasma Insulin (pg/mL) ± SEM at Intervals for 24 Months in Four Groups of Rats*

	First Day of Study		1–3 Months		4–6 Months		7–9 Months		10–12 Months		13–15 Months		16–18 Months		19–21 Months		22–24 Months	
Group	N	Mean ± SEM	N	Mean ± SEM	N	Mean ± SEM	N	Mean ± SEM	N	Mean ± SEM	N	Mean ± SEM	N	Mean ± SEM	N	Mean ± SEM	N	Mean ± SEM
NC	116	525 ± 6.3	116	523 ± 8.6	105	540 ± 9.1	98	492 ± 6.4	113	479 ± 5.3	106	440 ± 10.3	91	417 ± 7.0	76	394 ± 8.9	42	389 ± 12.4
DC	273	96 ± 6.8*	272	93 ± 6.7*	245	100 ± 8.2*	198	105 ± 7.2*	156	87 ± 7.3*	134	106 ± 10.9*	84	102 ± 9.8*	43	83 ± 9.6*	28	110 ± 32.4*
PDT	182	94 ± 6.4*	171	504 ± 6.4	154	537 ± 7.2	129	522 ± 6.2†	106	498 ± 5.3	81	472 ± 7.4†	41	468 ± 6.5†	12	445 ± 6.3†	9	430 ± 7.8†
IT	92	97 ± 7.1*	92	496 ± 11.7	87	520 ± 19.5	87	376 ± 16.6*	79	307 ± 11.9*	41	329 ± 26.7*	28	317 ± 26.8*	4	300 ± 22.1*	3	170 ± 130.0*

* Significantly lower than NC ($p < 0.001$).
† Significantly higher than NC ($p < 0.001$).
NC = nondiabetic control rats.
DC = untreated diabetic control rats.
PDT = diabetic rats that received a syngeneic pancreaticoduodenal transplant.
IT = diabetic rats that received a syngeneic pancreatic islet transplant.

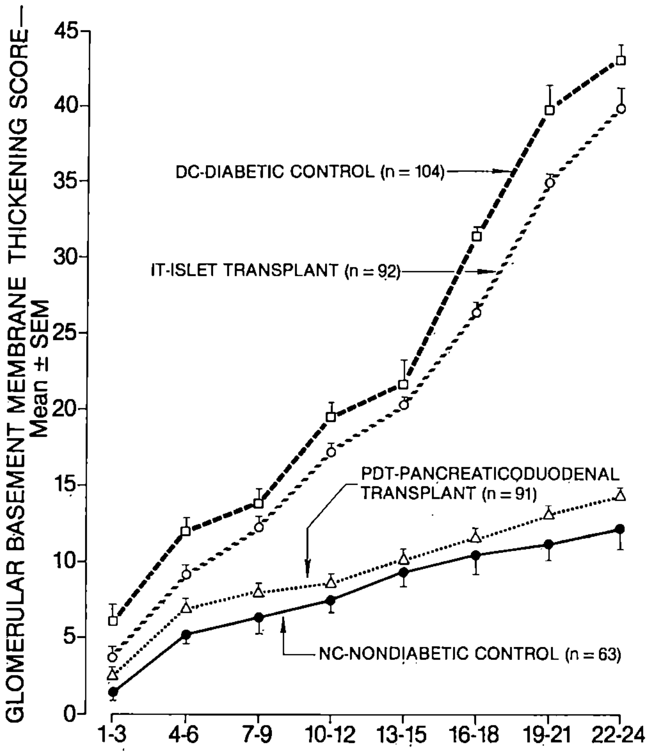

FIG. 1. Mean scores of glomerular basement membrane thickening in the four groups of rats.

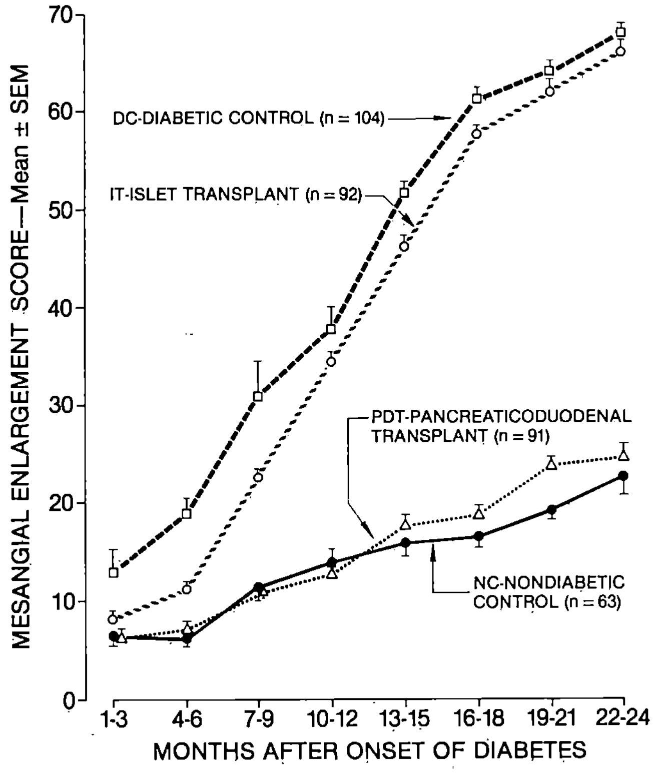

FIG. 2. Mean scores of mesangial enlargement in the four groups of rats.

cantly different from those in the nondiabetic controls. Pancreatic islet transplantation (Group IT) also produced a reduction of plasma glucose levels to the normal range during the first 2 months. However, from the third to the 24th months after induction of DM, mean plasma glucose concentrations in Group IT were significantly higher than those in the nondiabetic controls ($p < 0.001$), although the levels were well below those found in the diabetic controls.

Table 3 shows the results of monthly assays of plasma insulin. Mean plasma insulin concentrations in the untreated diabetic controls were depressed to 18–28% of the concentrations found in nondiabetic controls, but were restored permanently to normal or above by whole pancreas transplantation. On the other hand, although pancreatic islet transplantation restored plasma insulin levels to normal for the first 6 months of the study, there was a significant and progressive decline in plasma insulin concentrations below the normal range after the sixth month ($p < 0.001$).

Quantitative Morphologic Studies of Kidney Lesions

Glomerular basement membrane thickening (GBMT). Figure 1 shows the mean scores of glomerular capillary basement membrane thickening in the four groups of rats. In the nondiabetic controls, there was a gradual and progressive increase of GBMT during the 24 months of the study. GBMT in the untreated diabetic controls was significantly greater than in the nondiabetic controls at every time interval ($p < 0.001$), and the rate of increase was more rapid. Pancreaticoduodenal transplantation prevented abnormal GBMT. Mean scores in Group PDT were not significantly different from those in Group NC at any time. Pancreatic islet transplantation did not prevent the abnormal GBMT associated with DM. At all time intervals, mean scores of GBMT in Group IT were significantly greater than in Group NC ($p < 0.001$), but were not significantly different from those in Group DC.

Mesangial enlargement. Mean scores of mesangial enlargement in the four groups of rats are shown in Figure 2. As with GBMT, there was gradual ME over 24 months in the nondiabetic controls. Pancreaticoduodenal transplantation produced ME scores that were not significantly different from those found in Group NC. In contrast, beginning after 3 months of untreated DM, there was highly significant ME compared with that found in nondiabetic rats ($p < 0.001$), and pancreatic islet transplantation did not slow the rate at which ME developed. Mean scores of ME in Group IT were abnormal after the third month of the study, and were not significantly different from those in Group DC after the ninth month.

Bowman's capsule thickening (BCT). Figure 3 shows the mean scores of Bowman's capsule thickening in the four groups of rats. BCT was highly abnormal in the diabetic controls compared with that of the nondiabetic controls at all time intervals ($p < 0.001$). Pancreaticoduodenal transplantation prevented abnormal BCT throughout the 24-month study period. Pancreatic islet transplantation did not slow the rate of BCT associated with DM. Mean scores in Group IT were not significantly different from those in Group DC.

Armanni-Ebstein Lesions (A-E). Figure 4 shows the mean scores of A-E lesions, which consist of vacuolization and distention of the cells of the renal tubules, presumably due to glycogen accumulation.[20,36] No A-E lesions were found in normal control rats until 16–18 months, and few lesions were seen thereafter. Similarly, no A-E lesions were found at any time in rats with pancreaticoduodenal transplants. In contrast, there was a progressive increase in A-E lesions over 24 months in both the diabetic controls and the rats with islet transplants. After the sixth month, there were no significant differences in mean A-E scores between Group IT and Group DC.

Tubular protein casts (PRO). Figure 5 shows the mean scores of PRO in the four groups of rats. Normal control rats did not have any PRO until 10 months after entry into the study and then had a small but progressively increasing incidence of this abnormality. Mean scores of PRO in rats with pancreaticoduodenal transplants were not significantly different from those in normal control rats at any time. Untreated diabetic controls had a significant number of PRO at 1–3 months, and mean scores of PRO increased progressively over the 24 months of study. Islet transplantation did not prevent PRO; mean scores of PRO in Group IT and Group DC were not significantly different after the sixth month.

Discussion

Previous studies in our laboratory demonstrated that syngeneic pancreaticoduodenal transplantation performed soon after induction of alloxan diabetes in young rats, produced precise, life-long control of the metabolic disorders of DM.[37] Severe DM recurred when the pancreas graft was removed after 1–2 years. Furthermore, in quantitative morphologic studies conducted according to a "blind" protocol, we found that abnormal GBMT[38] and ME[39] in the kidney of alloxan-diabetic rats were prevented for life by whole pancreas isografts. Additionally, in quantitative morphologic studies completed recently, we observed that whole pancreas transplants performed at any time from 6–21 months after induction of alloxan diabetes were consistently capable of reversing severe ME.[40] No other long-term met-

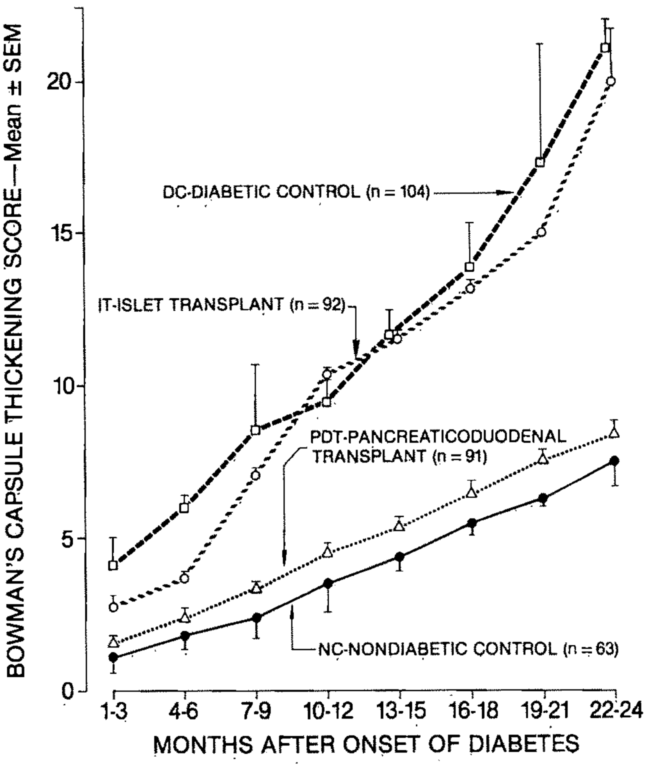

FIG. 3. Mean scores of Bowman's capsule thickening in the four groups of rats.

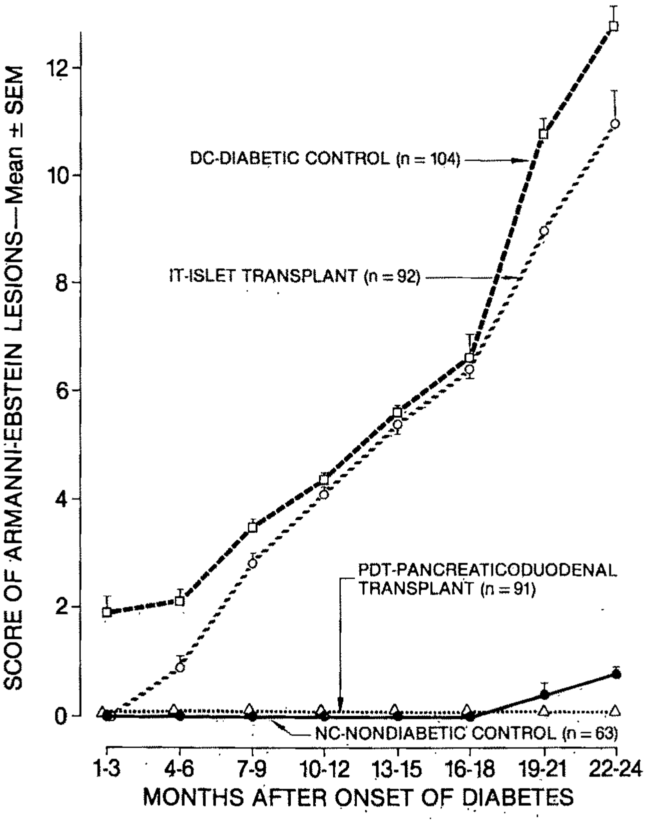

FIG. 4. Mean scores of Armanni-Ebstein lesions of the renal tubules in the four groups of rats.

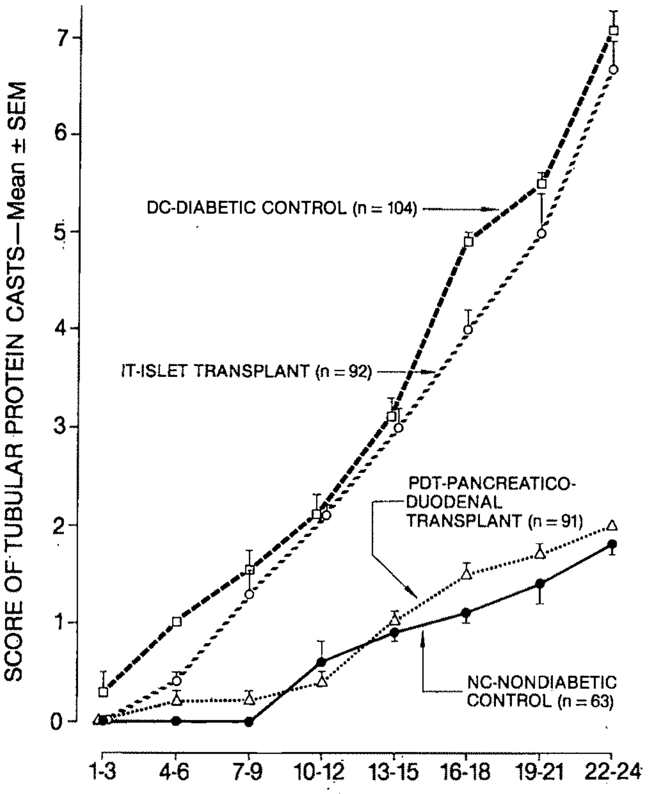

FIG. 5. Mean scores of tubular protein casts in the four groups of rats.

abolic studies or quantitative morphologic studies involving whole pancreas transplantation have been reported. Metabolic and morphologic investigations are being conducted in patients with IDDM who have had whole pancreas transplantation,[41] but the results are inconclusive because of short periods of observation and the small number of subjects available for study.

The results of the current investigation confirm and extend our previous observations with regard to whole pancreas transplantation. Pancreaticoduodenal isografts produced tight metabolic control for life and prevented all of the major kidney lesions of DM for 2 years. The kidney of diabetic rats that received pancreaticoduodenal transplants was not different in any respect from the kidney of age-matched nondiabetic controls.

In contrast to the paucity of work on whole pancreas transplantation, a number of studies have been reported of the effects of pancreatic islet transplantation on kidney lesions in rodents with chemical DM.[42–56] However, these studies have been short-term investigations conducted in a small number of animals, and only six have used quantitative morphologic methods and a "blind" protocol. One of these six quantitative studies reported prevention of GBMT in mice 6 months after islet transplantation,[51] and one study showed reversal of ME in rats 2 months after islet transplantation.[52] The other four quantitative studies reported failure of islet transplants to prevent[49] or reverse[50–52] either ME or GBMT.

The results of the current investigation indicate that pancreatic islet transplants were not capable of preventing the kidney lesions of DM. These findings are in accord with those of the majority of other investigations that used quantitative morphologic methods. Although the scores of the kidney lesions in rats with islet transplants were similar initially to those in the nondiabetic controls, beginning 4 months after transplantation and thereafter the scores in Group IT were significantly higher than those in Group NC ($p < 0.001$). Within 3 months after islet transplantation and thereafter, the severity of GBMT and BCT was similar to that found in diabetic controls, and within 6–9 months the severity of the other three lesions was similar in Group IT and Group DC. These results are in striking contrast to those obtained in rats with whole pancreas transplants.

The most likely explanation for the sharp difference in effectiveness between pancreaticoduodenal transplants and pancreatic islet transplants lies in how completely the two forms of transplantation achieved metabolic control. Whole pancreas transplantation accomplished precise metabolic control, manifested by continuously normal plasma glucose concentrations and normal or greater than normal plasma insulin levels. On the other hand, although islet transplantation produced normal plasma glucose levels for the first 2 months and substantially reduced hyperglycemia for life, plasma glucose concentrations were persistently abnormal after the third post-transplant month. Moreover, plasma insulin levels were subnormal after the sixth post-transplant month. Islet transplantation did not achieve complete metabolic control despite injection into the portal vein of 2000 islets, a dose that is considerably larger than that used by many other investigators.[57]

Improved but incomplete metabolic control has been a consistent finding in the short-term studies of pancreatic islet transplantation reported by other workers.[42,45,51,55,56,58–63] Specifically, normoglycemia was not achieved in a substantial number of animals with islet transplants, and those that were normoglycemic initially often had recurrence of hyperglycemia within 3–12 months. Moreover, plasma insulin levels consistently remained below normal, and the results of oral and intravenous glucose tolerance tests did not return to normal. Thus, even in short-term studies, pancreatic islet transplantation has not achieved precise metabolic control.

The same is true of artificial insulin delivery devices.[64,65] In patients with IDDM, insulin pump therapy has been shown to lower plasma concentrations of glucose and to correct abnormalities of amino acids, lipids, catecholamines, and growth hormone, but it has not accomplished long-term normoglycemia.[64,65] A number of recent studies have reported progression of nephropathy[21–23] and retinopathy,[24–32] and failure to improve neuropathy[32] during insulin pump therapy, perhaps because metabolic control has not been sufficiently precise to reverse the diabetic lesions.

The development and progression of diabetic nephropathy have not been prevented by conventional treatment with insulin injections and diet.[8–10] Nephropathy often develops in normal kidneys transplanted into diabetic recipients for end-stage renal failure, despite concerted efforts at metabolic control with conventional therapy.[66–69] Our previous findings that whole pancreas transplantation is capable of preventing GBMT and ME, and our current demonstration that pancreaticoduodenal transplants are effective in preventing all renal lesions of experimental DM, suggest that whole pancreas transplantation may be indicated in patients with end-stage diabetic nephropathy who require kidney transplantation and, therefore, must be given immunosuppression therapy for life. The outlook for the usefulness of pancreatic islet transplantation appears less promising.

Acknowledgments

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Discussion

Dr. John S. Najarian (Minneapolis, Minnesota): I want to congratulate the author on a very nice presentation of studies that we have followed with interest over the years.

I am, at one point, however, concerned about the conclusions that Dr. Orloff has reached. Therefore, I would like to state a few facts and ask a couple of questions.

In 1974, in the journal *Diabetes,* we showed that syngeneic islets, when transplanted to rats, can prevent, as well as reverse, the lesions of experimental diabetes in the kidney. This finding was reported in a syngeneic rat system in which the recipient rat was made diabetic with streptozotocin, a different form of beta cell poison than alloxan. This reversal was complete for diabetic lesions, which occurred within 3 months of streptozotocin treatment. However, if we waited 6–9 months, we could not reverse the lesions, which now became collagen-filled and irreversible. In its early and proliferative stages, however, the mesangial matrix material, which is the *sine qua non* of this lesion, could be reversed.

In 1975, armed with this information, we progressed to treating 20 patients who were Type I diabetics with allogeneic islets. We transplanted them with what we believed were enough islets, and yet, in each instance, we were only able to reduce their insulin requirements but never cure a single patient (insulin independence).

We temporarily gave up on this technique and went back into the clinical arena to perform segmental organ transplantation of the pancreas, as we had done initially in 1966 with whole organ pancreaticoduodenal transplants. Since 1978, we have performed 185 segmental or whole organ pancreas transplants.

At the same time we were puzzled with what happened to the transplanted islets in the previous clinical series. Was it a fact that we did not technically transplant viable islets, or was the lack of success due to immunologic rejection?

To determine which phenomenon was responsible for this failure, we investigated a series of patients with chronic small duct pancreatitis. We removed their pancreases, isolated the islets, and gave them back their own (autologous) islets, so there could be no immunologic consequences.

Under those circumstances, even though the number of islets was limited, half of these patients did not require further insulin, and currently, we have seven patients on isolated autogenous islets transplanted to the liver who do not require insulin and have excellent metabolic control. Our technique, therefore, was good; therefore, there must be immunologic problems that need to be solved to make islet allotransplantation successful.

Dr. Sutherland and I then went on and did 185 pancreatic organ transplants, whose results we presented to this Association, and clinically 60% of these transplants have worked very well. With pancreas transplants, we have seen partial reversal of triopathy; the renal lesions, the retinal lesions, and the neurologic lesions.

It is tempting to hope that the islets would work because, in fact, it would involve less surgery. In addition, you have enough islets so that you could treat more than one patient with the islets obtained from a single cadaveric donor.

It has been shown by various groups that you can transplant islets and achieve a completely normal glucose tolerance curve. This has been shown by David Sharp in St. Louis, Gus Nossal's group in Australia, Conrad Federle in Germany, and John Paul Squifflet in Brussels. All of these investigators have shown that with islets they can get normal glucose tolerance curves and can prevent the lesions that Dr. Orloff observes with animals that receive pancreatic transplants.

Thus, what has happened in the Orloff experiment with islet transplantation? We have found that when you put islets into the liver you lose about half of them. Therefore, we increased the number of islets transplanted sufficiently enough to get equivalent numbers of islets to those that we transplanted with whole organ pancreas transplants.

When we did that, there was no difference between the results of pancreatic organ transplants and islet transplants.

My question to Dr. Orloff is: how did you measure the amount of islets or insulin content that you had in the liver? In addition, even the slightest bit of species difference with islets would show the kind of erosion that he reported with the loss of islets with time. What species did you use and what combinations?

Dr. Keith Reemtsma (New York, New York): The question posed by Dr. Orloff is of central importance, and in his studies, islet transplants do not work well. However, other investigators have found that islet transplants can, in the long run, produce normal metabolism and reversal of the vascular diabetic changes, as measured by renal function and morphology.

The important question here is why, under the circumstances of this study, islet transplants do not function well. I would agree with Dr. Orloff that the most likely explanation for the vascular changes is the incomplete reversal of the metabolic state. But why? The pattern of failure suggests an inhospitable environment for the transplanted islets. Perhaps Dr. Orloff could comment on the liver pathology, as alloxan produces periportal fibrosis, and this might interfere with islet function.

These studies confirm that whole pancreas grafting is effective, and it results in hyperinsulinemia. The eventual role of islet transplants, however, remains unanswered.

Dr. Robert J. Corry (Iowa City, Iowa): I compliment Dr. Orloff on an excellent paper regarding an important issue; that is whether or not successful pancreatic transplantation can prevent or stabilize the devastating secondary complications of Type I diabetes. In his study, rats who received islets did not achieve normal glucose control, suggesting either that an insufficient supply of islets was administered or something happened to them in the first few months, such that normal glucose control could not be achieved. On the other hand, whole organ pancreatic transplantation resulted in normal glucose metabolism and prevented complications.

With regard to whole organ grafting we have reasons to be optimistic as a result of evidence emerging from a few U.S. and European pancreas transplant programs. In Stockholm, Carl Groth has shown prevention of the mesangial thickening in the glomeruli in patients who received combined kidney and pancreas grafts compared with another group of patients transplanted at the same time, namely diabetic recipients who received kidneys only. All patients who received kidneys and were followed after 3 years had microscopic changes of diabetes in the glomerulus, whereas none of the patients who received combined kidneys and pancreases had any degree of mesangial thickening.

In addition, Walter Land in Munich has shown some evidence of reversal of neuropathy as well as vasculopathy. Donald Dafoe in Michigan has presented some interesting data showing that blood lipids are significantly lowered in patients who have received successful pancreas grafts.

I would like to show a few slides indicating that whole organ transplantation of the pancreas does not necessarily preclude successful liver donation. This illustration shows the blood supply of both organs dissected. Essentially the gastroduodenal artery is ligated and the splenic artery is divided a few millimeters from its origin on the hepatic artery. The superior mesenteric artery is divided near the pancreas. The portal vein is divided as it exits the pancreas. In this way the blood supply for the donated liver will be normal, namely the aortic patch and entire portal vein go with the liver. Extension grafts are placed on the pancreas under ice by taking a segment of donor iliac artery with both branches. The internal iliac artery is then joined to the superior mesenteric artery and the external iliac artery is joined to the splenic artery. Donor iliac vein is then used to extend the portal vein. These extension grafts are placed under iced solution so the ischemic time is not extended very much.

Dr. Thomas E. Starzl (Pittsburgh, Pennsylvania): This is a grand organization that we belong to and the prestige of the organization is so great that a paper presented here is apt to be construed as the last word. If we really accept this paper on absolutely face value, this could be the death knell of islet cell transplantation. It is in that context that I want to make a few comments and this is where I am inclined to be in agreement with Dr. Najarian.

Solid pancreas transplantation in principle as practiced successfully by Dr. Orloff and by others at Minnesota and elsewhere, is different than almost anything else we do. If we transplant the kidney, there is no carrier tissue that comes along with the graft. It is a simple, straightforward intellectual exercise. If there is any carrier function that comes with the kidney, it might be the production of erythropoietin. The heart is a simple pump, and with the liver, practically every cell does something that is essential for the survival and health of the recipient. In the case of the pancreas we are transplanting an organ in which if we transplant 100 g, almost all of that is tissue, which, first of all, is not needed, and second, is a nuisance. That extra tissue accounts for almost all the morbidity and mortality of whole organ pancreas transplantation, which is considerable.

What are the options? One of the options is the procedure that fared so poorly in Dr. Orloff's comparison. I do not doubt for a moment his conclusions, but I must say that I still have hopes for islet cell transplantation. I hope that this paper, as fine as it is, will not cause funding to be precluded for islet cell research or efforts to be stopped by some of those groups that are still making those efforts such as Scharp in St. Louis, Lafferty and Weil from Colorado, Mintz and Miller from Miami, and possibly others including Sutherland of Minnesota and Barker et al. from Pennsylvania.

Other options have to be carefully explored because of the deficiencies not only of whole organ transplantation, but also of islet cell transplantation. One possibility might well be gene splicing, in which cells are endowed with the ability to produce insulin. Anything that could move us in that direction would be valuable and certainly would be worth pursuing.

The annals of history, as my friend, Mark Ravitch, has reminded me often, are replete with missed opportunities. I could recount many but these would reveal my age. We do not have to go much farther back than last month's *New England Journal of Medicine* in which there was a report from Mexico about successful transplantation of adrenal tissue into the brain for the treatment of neuropsychiatric disorders. This was a procedure that had been thoroughly discredited in previous Scandinavian trials, but that now holds great promise instead. I hope that islet transplantation or some analogue or derivative of that procedure is not actually dead.

DR. MARSHALL J. ORLOFF (Closing discussion): I am honored to have this work discussed by some of the giants in this field, and there is no doubt that they are the giants. Keith Reemtsma was working on pancreas transplantation when I was just a boy, and he reminded me of that before he got up to discuss my paper. He has made enormous contributions to this field. As to John Najarian, whenever I present a paper, he always gets up and says: "It is a very nice piece of work, but we did that back in 1970." And he is sometimes right. His experimental and clinical work and that of his group, David Sutherland and the others, has been monumental in the field of pancreas transplantation. I guess you would have to call the Minnesota group the leading pancreas transplantation group in the world. Of course, I cannot even begin to describe what Tom Starzl has done for everything in transplantation. It is awesome. I hate to think about it because I feel so inferior after thinking about all the things that he has done. Rob Corry is a relative newcomer, the new kid on the block, but the results that they are having in Iowa with clinical transplantation of the pancreas are extremely promising and they have developed very rapidly. They certainly have my respect.

The main issue I believe, and it is a critical issue, is what degree of metabolic control is required to prevent and/or reverse the lesions of diabetes, not just in the short term, but in the long term. Our experimental data suggest, and in fact the clinical data including the data on insulin pump therapy suggest, that the control must be very precise and must be of long duration. Brief periods of control for a few months do not really mean a lot. It has to be very precise and prolonged.

As far as we can tell, at least to this point, the most precise metabolic control comes from transplanting the whole pancreas. It is the only form of endocrine pancreas replacement therapy that has produced complete and prolonged metabolic control.

Regarding the comments of John Najarian, I have the following response: (1) The 1974 report of his group in *The Journal of Experimental Medicine*, in which kidneys from 11 diabetic rats were transplanted into normal rats, did not show statistically significant reversal of mesangial matrix thickening. Furthermore, this was a very short-term, nonquantitative study in which the kidneys were transplanted after only 6 months of diabetes and then were studied only 2 months later. I do not believe any conclusions from this study, positive or negative, are possible. (2) As to his six patients who have received autologous islets, the problem with all of these case reports is that the patients have not had long-term, well-established diabetes before islet transplantation, and there is always the question of whether the patients would have had diabetes without the autologous islet transplantation. The hard facts are that there is not a single case of successful, prolonged relief of diabetes mellitus among the more than 100 diabetic patients who have received islet transplants. (3) Regarding John's statement that many have shown completely normal GTT's following islet transplantation, the facts are that if one examines the literature carefully, one will be hard-pressed to find *long-term*, clearly documented normalization of the GTT. For example, Renold's group and Barker's group both found that the GTT remained abnormal, and numerous studies, including those from Dr. Najarian's own institution (Steffes et al., Vialettes et al.) have shown failure of plasma glucose and insulin levels to normalize both initially and in the long term. (4) John asked: Is it possible that our islets were being rejected? We used highly inbred Lewis rats. We have shown that these rats accept transplants of skin, whole pancreas, liver, intestine, stomach, spleen, and heart without developing clinical or histologic evidence of rejection. There was no histologic evidence whatsoever of immunologic rejection of our islet transplants. (5) Finally, Dr. Najarian asked how we measured the volume of islets transplanted. We counted the number of islets microscopically in an aliquot of the islet suspension. We transplanted approximately 2000 islets, which is more than the number used by the vast majority of workers. For example, in intraportal transplants, Kipnis, Lacy et al. used 350–1000 islets, Barker et al. used 400–500 islets, and Federlin et al. used 500–800. There is no question that our transplants were successful, since they produced normal plasma glucose and insulin levels for the first several months. Measurement of insulin output from the liver is not a good way of quantitating the adequacy of the transplant, unless repeated measurements over a long period are made, and no one has done that.

Keith Reemtsma raised the possibility that alloxan might cause periportal fibrosis that interferes with the viability of the islets. We have studied several thousand rats with alloxan diabetes and have never seen any evidence of periportal fibrosis or hepatic changes. Moreover, our islet transplants were very viable for the first several months. However, as others such as Barker et al. have observed in streptozotocin diabetes, there is a progressive loss of islets after initial metabolic control, I believe because they do not bring their own supply of blood vessels and have a very tenuous existence. As time goes by, the islets are easily lost, perhaps as a result of even transient reductions in hepatic blood flow and oxygen supply.

Tom Starzl made an inspirational statement about continued funding for research in islet transplantation. I do not believe there is anything to fear. Having worked in the field of portal hypertension for many years, I have often observed that nothing dies except the patients.

Although I have considerable doubt about the ultimate success of islet transplantation, there is no question that continuing research is warranted along all avenues that could conceivably help the millions of patients who suffer from diabetes. Moreover, islet transplants have provided and will continue to provide important information about many aspects of diabetes and its treatment. An understanding of islet physiology, islet immunology, and prevention of islet rejection are but a few of the potential and actual benefits of islet transplant research.

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Continued on page 36A

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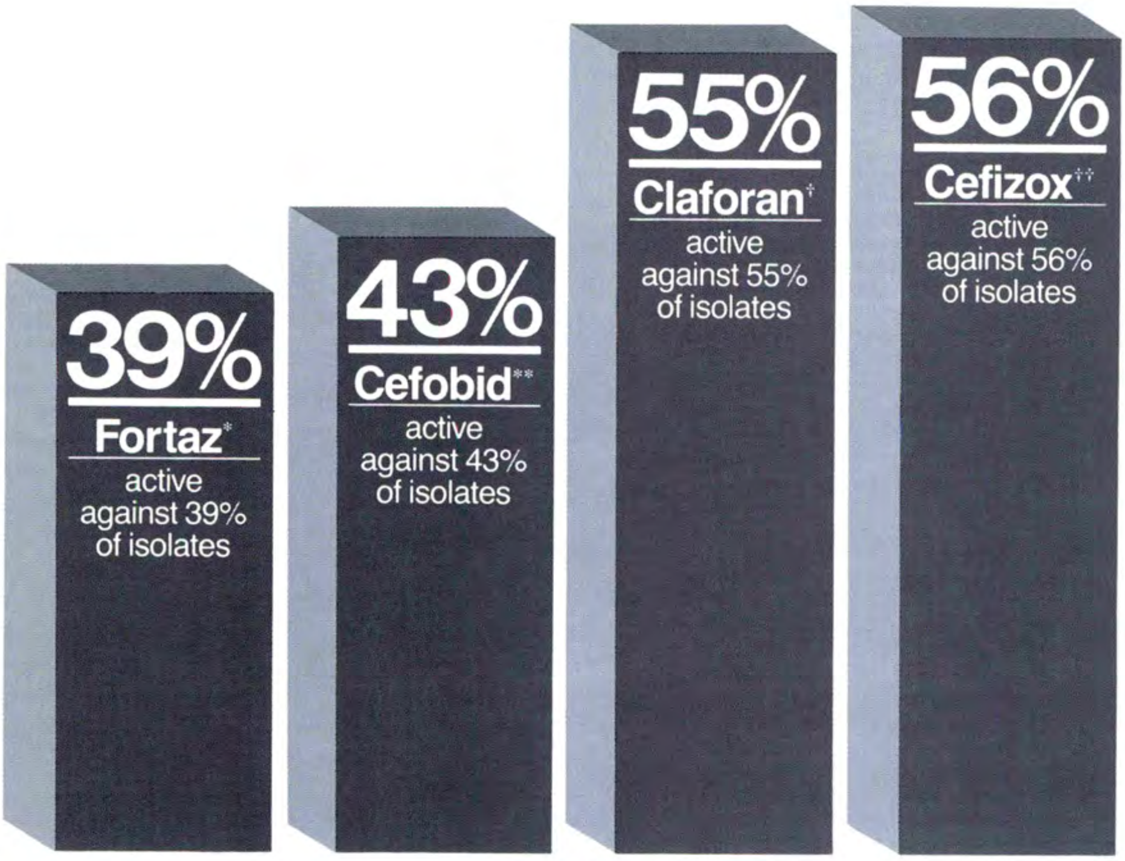

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GENITOURINARY INFECTIONS. Urinary tract infections caused by *E. coli*, *Klebsiella* species, *Proteus mirabilis*, indole-positive *Proteus* (i.e., *P. morganii*, *P. rettgeri*, and *P. vulgaris*), and *Providencia* species. Uncomplicated gonorrhea due to *Neisseria gonorrhoeae* (penicillinase and non-penicillinase producing).

INTRA-ABDOMINAL INFECTIONS, including peritonitis and intra-abdominal abscess, caused by *E. coli*, *Klebsiella* species, *Bacteroides* species including the *B. fragilis* group,§ and *Clostridium* species.

GYNECOLOGICAL INFECTIONS, including endometritis, pelvic cellulitis, and pelvic inflammatory disease, caused by *E. coli*, *N. gonorrhoeae* (penicillinase and non-penicillinase producing), *Bacteroides* species including the *B. fragilis* group,§ *Clostridium* species, *Peptococcus* species, *Peptostreptococcus* species, and group B streptococci.

SEPTICEMIA caused by *Strep. pneumoniae* (formerly *D. pneumoniae*), *Staph. aureus* (penicillinase and non-penicillinase producing), *E. coli*, *Klebsiella* species, and *Bacteroides* species including the *B. fragilis* group.§

BONE AND JOINT INFECTIONS caused by *Staph. aureus* (penicillinase and non-penicillinase producing).

SKIN AND SKIN STRUCTURE INFECTIONS caused by *Staph. aureus* (penicillinase and non-penicillinase producing), *Staph. epidermidis*, streptococci (excluding enterococci, e.g., *Strep. faecalis*), *E. coli*, *P. mirabilis*, *Klebsiella* species, *Bacteroides* species including the *B. fragilis* group,§ *Clostridium* species, *Peptococcus* species, and *Peptostreptococcus* species.

Although appropriate culture and susceptibility studies should be performed, therapy may be started while awaiting these results. Cefoxitin is not active *in vitro* against most strains of *Pseudomonas aeruginosa* and enterococci (e.g., *Strep. faecalis*) and many strains of *Enterobacter cloacae*. Methicillin-resistant staphylococci are almost uniformly resistant to cefoxitin.

Contraindications: Previous hypersensitivity to cefoxitin and the cephalosporin group of antibiotics.

Warnings: BEFORE THERAPY IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE PREVIOUS HYPERSENSITIVITY REACTIONS TO CEFOXITIN, CEPHALOSPORINS, PENICILLINS, OR OTHER DRUGS. GIVE WITH CAUTION TO PENICILLIN-SENSITIVE PATIENTS. ANTIBIOTICS SHOULD BE ADMINISTERED WITH CAUTION TO ANY PATIENT WHO HAS DEMONSTRATED SOME FORM OF ALLERGY, PARTICULARLY TO DRUGS. IF AN ALLERGIC REACTION TO CEFOXITIN OCCURS, DISCONTINUE THE DRUG. SERIOUS HYPERSENSITIVITY REACTIONS MAY REQUIRE EPINEPHRINE AND OTHER EMERGENCY MEASURES.

Pseudomembranous colitis, from mild to life-threatening in severity, has been reported with virtually all antibiotics (including cephalosporins); therefore, it is important to consider its diagnosis when diarrhea develops in association with antibiotic use. Broad-spectrum antibiotics alter normal flora of colon and may permit overgrowth of clostridia; a toxin produced by *Clostridium difficile* is a primary cause of antibiotic-associated colitis. Mild cases may respond to drug discontinuance alone; in more severe cases, management may include sigmoidoscopy, appropriate bacteriological studies, fluid, electrolyte and protein supplementation, and use of a drug such as oral vancomycin; isolation of the patient may be advisable. Other causes of colitis should also be considered.

Precautions: *General*—Total daily dose should be reduced in patients with reduced urinary output due to renal insufficiency because high and prolonged serum antibiotic concentrations can occur from usual doses. Prescribe with caution in patients with a history of gastrointestinal disease, particularly colitis. Prolonged use may result in overgrowth of nonsusceptible organisms; repeated evaluation of the patient's condition is essential. If superinfection occurs, take appropriate measures.

Drug Interactions—Increased nephrotoxicity has been reported following concomitant administration of cephalosporins and aminoglycoside antibiotics.

Drug/Laboratory Test Interactions—High concentrations (>100 mcg/mL) may interfere with measurement of serum and urine creatinine levels by the Jaffé reaction and produce false increases of modest degree in creatinine levels reported; serum samples should not be analyzed for creatinine if withdrawn within 2 hours of cefoxitin administration. High concentrations may interfere with measurement of urinary 17-hydroxy-corticosteroids by the Porter-Silber reaction and produce false increases of modest degree in levels reported. A false-positive reaction for glucose in urine has been observed with CLINITEST‖ reagent tablets.

Carcinogenesis, Mutagenesis, Fertility Impairment—No long-term animal study has been performed on carcinogenic or mutagenic potential. Rat studies at approximately three times maximum recommended human dosage revealed no effects on fertility or mating ability.

Pregnancy Category B—Reproduction studies in rats and mice did not reveal teratogenic or fetal toxic effects, although fetal weights were slightly decreased. In rabbits, cefoxitin was associated with a high incidence of abortion and maternal death, neither considered teratogenic. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers—Excreted in human milk: Exercise caution.

Pediatric Use—Safety and efficacy in infants from birth to three months have not yet been established. In children three months and older, higher doses have been associated with increased incidence of eosinophilia and elevated SGOT.

Adverse Reactions: The most common adverse reactions have been local reactions following intravenous or intramuscular injection. Other adverse reactions have been encountered infrequently. *Local Reactions*—Thrombophlebitis with intravenous administration; pain, induration, and tenderness after intramuscular injections. *Allergic Reactions*—Rash (including exfoliative dermatitis), pruritus, eosinophilia, fever, and other allergic reactions including anaphylaxis. *Cardiovascular*—Hypotension. *Gastrointestinal*—Diarrhea, including documented pseudomembranous colitis during or after treatment, and, rarely, nausea and vomiting. *Blood*—Eosinophilia, leukopenia including granulocytopenia, neutropenia, anemia, including hemolytic anemia, thrombocytopenia, and bone marrow depression. A positive direct Coombs test may develop in some individuals, especially those with azotemia. *Liver Function*—Transient elevations in SGOT, SGPT, serum LDH, and serum alkaline phosphatase. *Renal Function*—Elevations in serum creatinine and/or blood urea nitrogen levels and, rarely, acute renal failure.

Note: In group A beta-hemolytic streptococcal infections, therapy should be maintained for at least 10 days to guard against the risk of rheumatic fever or glomerulonephritis. In staphylococcal and other infections involving a collection of pus, surgical drainage should be carried out where indicated. Intramuscular injections should be well within the body of a relatively large muscle such as the upper outer quadrant of the buttock (i.e., gluteus maximus); aspiration is necessary to avoid inadvertent injection into a blood vessel. The total daily dosage in infants and children should not exceed 12 grams.

How Supplied: Sterile cefoxitin sodium in vials, infusion bottles, and ADD-Vantage®# vials containing 1 gram or 2 grams cefoxitin equivalent and in 10-gram bulk bottles

§ *B. fragilis*, *B. distasonis*, *B. ovatus*, *B. thetaiotaomicron*, *B. vulgatus*

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Continued from page 31A

Private practice: Wanted general or thoracic surgeon, BC/BE, to join same, vascular training desired. Metropolitan city, S.C. with University affiliation. Please respond with curriculum vitae and references: **Box ANN9B, J.B. Lippincott Co., East Washington Square, Philadelphia, PA 19105.**

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The Department of Surgery of The Ohio State University is searching for board-certified general surgeons with specialty experience and interests in the following areas: Traumatology; Critical Care/Trauma; and Critical Care/Burn Care. Curriculum vitae should be sent to: **Department of Surgery, Office of the Chairman, N-711 Doan Hall, 410 W. 10th Avenue, Columbus, OH 43210.**

VASCULAR SURGEON—The Department of Surgery, Medical College of Pennsylvania is recruiting a board certified/eligible vascular surgeon for a full-time academic position. Responsibilities include patient care, research, medical student and resident instruction. Benefits and insurance included. **Apply to Division of Vascular Surgery, Medical College of Pennsylvania, Philadelphia, PA 19129.**

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Blood Flow in Colonic Anastomoses

Effect of Stapling and Suturing

RAPHAEL S. CHUNG, M.D., F.A.C.S.

From the Departments of Surgery, Veterans Administration Medical Center and State University of New York Health Science Center, Syracuse, New York

Sutureline blood flow was measured with laser Doppler velocimetry in colonic anastomoses created with the stapler, manual suturing, or a combination. Blood flow was always reduced in the sutureline compared with normal mucosa. Of all the anastomoses studied, tight stapling reduced sutureline blood flow the most, whereas the two-layered manual anastomosis or stapling reinforced with sutures were somewhat less ischemic. Stapling adjusted to bowel wall thickness impaired flow only moderately. It was possible with practice to outperform the stapler by single-layered manual anastomosis using fine sutures. In humans, stapled ileocolostomy had a higher sutureline blood flow than the two-layered manual anastomosis. In view of the existing clinical experience of safe stapling without adjustment for bowel wall thickness, a low sutureline blood flow is probably tolerated to a considerable degree in humans. However, this study clearly shows that tight stapling can reduce sutureline blood flow unduly, whereas superior blood supply can be attained by attention to staple closure height relative to bowel wall thickness.

THE BLOOD SUPPLY to the sutureline, believed to be of fundamental importance in healing of anastomoses, is difficult to study because of logistical problems. The tension of suturing, a major variable that affects blood flow, is not easy to standardize. Also, the minute area of the sutureline does not lend itself readily to accurate flow measurements. In this study, stapling is used as a method of suturing at reproducible tension, with staple closure height adjusted according to tissue thickness. Sutureline blood flow is recorded with laser Doppler velocimetry, which provides a continuous recording in real time. By direct application of the fine laser Doppler probe to the narrow rim of tissue inside of the staple lines or on top of the manual sutureline, tissue blood flow of the area in question can be measured with confidence. The model was first tested for validity: the effect of tight stapling on sutureline blood flow was determined by this technique. The effect of manual suturing on anastomotic blood flow was then compared with that of stapling. The methodology was subsequently modified to study ileocolic anastomoses in patients.

Methods

Laser Doppler Velocimetry

The instrument (Laserflo BPM 403, TSI Inc., St. Paul, MN) uses an infrared laser (wavelength 780 nm, output 2 mW) with a penetration depth of 1 mm. The flow probe, 2.2 mm in diameter, contains fine optical fibers that conduct the laser to the tissue and carry the reflected light back to photodetectors. The reflected light undergoes a shift in wavelength due to the Doppler effect, the magnitude of the shift being proportional to the velocity of the red blood cells. To minimize motion artifacts, a holder modified from a micropositioner was used to hold the probe against the tissue at a standardized pressure of 8 g/cm^2. Transmitted respiratory and cardiac motion was reduced by resting the gut on a platform; when movement proved difficult to eliminate, the probe was coupled to the tissue with a miniature suction cup so that the probe and tissue moved together. Motion artifacts were in general recognizable as erratic readings that appeared on tracing as sharp irregular spikes. Duplicate readings were obtained from steady tracings lasting at least several minutes.

The instrument readout was in hertz × 10^2, a frequency measurement. The instrument manufacturer recommends conversion into mL/100 g/min by multi-

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Presented at the 107th Annual Meeting of The American Surgical Association, Palm Beach, Florida, April 21–23, 1987.

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TABLE 1. *Blood Flow in Colonic Anastomoses (Dog)**

Group	2 × Bowel Thickness	Staple Height	Control MBF	SBF	Percent Reduction	p
I	3.5 ± 0.5	3.4	28 ± 4 (36 ± 7)	16 ± 2 (23 ± 6)	43 (36)	<0.001† <0.05†
II	3.4 ± 0.5	1.7	31 ± 4	9 ± 1	71	<0.01‡
III	3.3 ± 0.5	3.3	28 ± 3	12 ± 2	57	<0.05‡
IV	3.2 ± 0.5	3.2 + suture	29 ± 4	13 ± 2	55	<0.05‡
V	3.5 ± 0.5	suture 1-layer	30 ± 4	22 ± 3	27	<0.01‡
VI	3.4 ± 0.4	suture 2-layer	29 ± 3	12 ± 2	59	<0.01‡

* N = 5, mean ± SE.
† MBF vs. SBF, paired t-tests.
‡ *vs.* Group I, unpaired t-tests.

MBF = mucosal blood flow, SBF = sutureline blood flow; flow units = mL/10 g/min; linear units = mm; figures in parentheses were obtained with the radiolabeled microsphere technique.[14]

plying with a conversion factor of 6, based on published experiments[1,2] and unpublished experiments. In our laboratory, 48 pairs of measurements of gastric and duodenal blood flow made simultaneously by the hydrogen gas clearance method and laser Doppler velocimetry were subjected to regression analysis. The correlation coefficient was 0.88 ($r^2 = 0.79$, $p < 0.0001$). In the range of 10–40 mL/100 g/min, the conversion factor was 5.11. This factor was used to convert the instrument readout into mL/100 g/min in the current study. The validity of this technique of measurement has also been extensively documented in the literature.[1-5]

The superior reproducibility of laser Doppler velocimetry over other techniques is in some measure due to averaging measurements over time. Although all other techniques yield "spot" readings and are subject to the spontaneous variation of the circulation, the readout of the laser Doppler flowmeter represents a large number of instantaneous measurements averaged by the computer. In this study a continuous recording of the readout over several minutes was further averaged.

Setting the Staple Closure Height

The thickness of the sigmoid colon was measured at the thickest portion (over the tinea) with a specially calibrated spring-loaded caliper delivering a pressure of 100 g/cm^2. In the dog this value was between 2.8 and 3.7 mm, representing the thickness of two layers of the bowel wall. The staple closure height was set according to this reading, using a stapler (ILS, Ethicon, Somerville, NJ) with provision for such adjustment in the form of a dial, specially calibrated to read up to 3.7 mm. The dialed gap was further checked with a micrometer before use; in all instances the reading was within 10% of the dialed measurement. At the tallest setting (3.7 mm) the closed staples assumed the "O" formation rather than the usual "B" formation.

The Anastomosis Model

Under pentobarbital anesthesia and controlled ventilation, a 2-cm colotomy was made in the sigmoid colon between stay sutures in large mongrel dogs. The mucosal blood flow was determined with the laser Doppler probe at the site selected for stapling or manual suturing, usually 4–5 cm away from the colotomy. The mesenteric arcade at the site of anastomosis was not disturbed. A 25-mm external diameter circular stapler was inserted *via* the colotomy, and after tying a ligature around the shaft, it was closed and fired at a staple closure height determined by bowel wall thickness. After removal of the stapler, the rim of the anastomosis was exposed and blood flow was measured by direct application of the laser Doppler probe to the narrow rim inside of the staple lines. In sutured anastomosis, the bowel was transected with intact mesenteric attachment and without using electrocautery. The blood flow 1 mm from the edge (edge flow) was then measured; the edge flow was found to be identical to the mucosal flow before transection. The least suture tension compatible with a mechanically sound anastomosis was used. After completion of the anastomosis, the flow probe was applied to the mucosal ridge in the space between the suture loops. To verify that the laser Doppler probe was in fact measuring the flow in the rim of the anastomsis, the radiolabeled microspheres technique was used simultaneously to measure sutureline blood flow in one group of dogs (Group I), excising blocks of tissue at the staple line 1 mm thick (measured from the lumen) for counting. The measurements were in accordance (see Table 1).

Experimental Protocol

In Group I, the staple closure height was set equal to the thickness of the bowel walls to be stapled, whereas in Group II, the setting was at half of this value. In Group III, the bowel was first transected without devascularization. Pursestring sutures were inserted at the open ends and stapling was accomplished by the usual technique, taking care to avoid gathering excess tissue by the pursestrings. Group IV was identical to Group I but an additional seromuscular layer of interrupted 5-0 silk was added. In Group V, a single-layered anastomosis was accomplished with interrupted sutures of 5-0 silk, in such a manner as to impede flow the least, in the judgment of the operator. In Group VI, after bowel transection, a double-layered anastomosis was performed using 4-0 chromic catgut for an inner running layer followed by an outer layer of 5-0 interrupted silk sutures.

Human Studies

In patients who had right hemicolectomy, informed consent (approved by the Institution Review Board for the protection of study subjects) was obtained for randomization into stapling and suturing groups. To avoid an "insertion" colotomy, end-to-side ileocolic anastomosis was made, inserting the stapler *via* the transected transverse colon, and the sutureline blood flow (colonic side) was measured *via* the same open end of the colon before closure, using a sterilized probe. The staple closure height was set at 75% of the combined bowel wall thickness to avoid bleeding problems. The average setting was 2.4 mm. The manual anastomosis was done by a conventional two-layered end-to-end technique, with an inner running 4-0 chromic catgut suture and an interrupted outer layer of fine silk, modified so as to allow the sutureline flow to be measured after completion of three fourths of the anastomosis (both layers).

Results

Effect of Stapling on Blood Flow

A stapled anastomosis created with staple closure height equal to the thickness of the two bowel walls is theoretically the least ischemic possible. The blood flow of the narrow rim of mucosa obtained under this circumstance was only 56% of the normal mucosal flow, or a 43% reduction ($p < 0.005$) (Table 1). A 36% reduction was recorded by the radiolabeled microsphere technique used simultaneously. Allowing for the different principles of measurement, the agreement was remarkably close. In three of the five anastomoses, significant bleeding occurred requiring manual tamponade before blood flow could be measured. The staples appeared to be somewhat "loose" and not perfectly aligned as in the stitches of a sewing machine, but no macroscopic leakage was demonstrable. The staples were generally in the "B" configuration, although the legs were separated from the body of staple by a gap of about 1 mm.

Effect of Tight Stapling on Blood Flow

When staple closure height had been set to half of the combined thickness of the bowel walls, the sutureline blood flow was reduced by 69% of mucosal flow ($p < 0.001$, paired t-test). This reduction was greater than that in Group I ($p < 0.01$, unpaired t-test).

In Group III the staple closure height was the same as for Group I, but the bowel was first transected and pursestring sutures were applied to both open ends. The flow reduction at the staple line was 57%, greater than that in Group I ($p < 0.05$, unpaired t-test).

Effect of Manual Suturing on Blood Flow

Double-layered suturing (Group VI) resulted in 59% reduction in blood flow, even when surgical technique of the best tradition was followed. The anastomosis was significantly more ischemic than the stapling in Group I ($p < 0.01$). The least impairment of flow was attained after several attempts with a single-layered manual anastomosis, using fine sutures and meticulous attention to tying tension (Group V, 27% reduction; Group V < Group I, $p < 0.01$, unpaired t-test). Even though no leaks were demonstrable grossly, some of these anastomoses appear mechanically precarious to the surgeon accustomed to more secure suturing.

Addition of a layer of interrupted fine sutures to an appropriately stapled anastomosis (Group IV) exacted a toll on the blood flow, although the difference (Group I *vs.* Group IV, $p > 0.05$) was not significant. The net effect of this anastomosis appeared to be similar to a two-layered manual suturing (55% *vs.* 59% reduction).

Human Data: Stapled Versus *Two-layered Manual Ileocolic Anastomosis*

The mucosal rim (colon side) of stapled end-to-side ileocolostomy was compared with the end-to-end ileocolic manual anastomosis (colonic mucosa) in five patients who had elective right colectomy for carcinoma, with similar extent of resection of the mesentery. There was no dilatation involving the parts anastomosed, and preoperative preparations were the same. Even though the configurations were different, in both groups the mesenteric attachment of the bowel was left intact right up to the anastomotic line. The results in all five patients are listed in Table 2. The three stapled anastomoses had less reduction in blood flow, although the small sample size precluded meaningful statistical analysis. No sutureline bleeding occurred in either group.

Discussion

The two basic considerations in the surgical technique of intestinal anastomosis are mechanical integrity and tissue viability. If the suturing is too loose, the anastomosis is mechanically leaky, and if the suturing is too tight, tissue viability is jeopardized by ischemia. Sound surgical technique must score well on both counts.

The mechanical integrity of stapled anastomosis is well established.[6-8] Stapled anastomoses, as do well-constructed, double-layered, hand-sewn anastomoses,

TABLE 2. *Blood Flow in Ileocolic Anastomoses (Human)*

Patient	Technique	Control MBF	SBF	Percent Reduction
1	Stapled (2.4 mm)	41	17	58
2	Sutured	38	11	71
3	Stapled (2.6 mm)	33	17	48
4	Sutured	48	15	69
5	Stapled (2.3 mm)	34	16	53

MBF = mucosal blood flow; SBF = sutureline blood flow; flow unit = mL/100 g/min.

withstand vigorous challenges such as prostigmine and castor oil administration. Even total obstruction caused by error in stapling may not disrupt the staple line.[8] Bursting strength studies,[9,10] which reflect the degree of healing as well, showed stapling to be superior.

The vascularity of stapled anastomosis is less well studied. Microangiography showed that small vessels do cross the staple lines, through the holes of the B formation of the closed staples.[8,11] There have been no quantitative blood flow studies to date, to the best knowledge of this investigator.

The current study shows that all suturing decreases blood flow, an almost self-evident truism. "Tight" stapling, as contrasted with "loose" stapling, decreases sutureline blood flow. Even though there is no tension data on manual suturing, it is reasonable to infer that tight suturing must have the same effect, a commonly held surgical belief. The "tight" stapling in this experiment may not be too tight by clinical standards, since most staplers have a fixed closure gap at 2 mm, even allowing that the human colon is somewhat thinner than the dog colon. However, some circular staplers currently used allow a minimum gap setting of 1 mm or so, when even lower anastomotic blood flow can be expected. Unduly tight closure of the stapler is instinctively eschewed by the experienced surgeon, but this may still constitute a pitfall to the unwary.

In the most ideal circumstances, when the staple closure height equals the bowel wall thickness, stapling reduced blood flow by 43%, significantly superior to conventional suturing in two layers (59% reduction) or stapling "reinforced" with suturing (55% reduction). However, good vascularity in stapled anastomosis is accompanied by a definite risk of sutureline bleeding, since the stapler makes a circular incision inside of the concentric staplelines, unlike manual suturing. Furthermore, excessively loose staples may be at risk from displacement causing uneven spacing and even leakage. It is likely that in manual suturing, the continuous running layer contributes more to the ischemia. The stapled anastomosis "reinforced" with sutures is in fact a three-layered affair, the resulting decrease in blood flow is not surprising.

The reason for decreased staple line blood supply in the technique using pursestring sutures is not clear. The gathered tissue by the pursestrings added bulk only in the core of the stapler, and the staple lines included only two layers of bowel. Some stretching of the bowel wall at the circumference of the stapler may conceivably have occurred as the "donuts" were being pushed inside the stapler during closure of the machine, thereby interfering with blood flow.

In an attempt to outperform the stapler with manual suturing, this investigator succeeded in the laboratory only after several attempts (and some practice) by using a single layer of fine sutures with meticulous attention to the tying tension, conditions not necessarily always fulfilled in clinical practice. The data support, at least in theory, that single-layered manual anastomosis is the least ischemic, recognizing that in practice it need not be so.

The human data of this study indicate that a somewhat lower sutureline blood flow was accomplished without significant bleeding, by adjusting the staple closure height to 75% of bowel wall thickness. The vascularity of the staple line (about 53% reduction) appeared to be superior to the conventional manual two-layered suturing (about 70% reduction). Such a height also conferred good mechanical security. It is likely that the different anesthetics and suture tensions used by different operators in these cases might account for the greater variance: a large number of cases would be required to discern statistically significant differences.

Although in the acute state, greatly reduced blood flow follows multilayered suturing or tightly stapled anastomosis, it is not known what compensatory mechanisms are triggered and what happens to the decreased blood flow in the hours or days after the operation. Ongoing chronic study in our laboratory shows that severe ischemia may be tolerated in stapled anastomoses without complication in the dog, provided it is not extreme. Other reports have also indicated that the course of focal ischemia (such as ligation of the arcade vessels) in the intestine of the dog is often unpredictable: it may progress to frank gangrene or have no apparent effect.[12,13] Data of ischemia in the dog are thus less likely to be of value as a clinical guide, and more human data are needed to establish a safe lower limit for sutureline blood flow.

The closure height of most circular staplers are nominally fixed, usually at 2 mm. A decade of clinical experience with this type of stapler demonstrated the relative safety of the 2-mm staple closure height for most gastrointestinal stapling. Since the thickness of the gut varies not only with individuals and anatomic regions but also with disease processes, the uniform closure height, although ideal sometimes, must also be relatively ischemic in others. This suggests that even in humans, tolerance of a certain degree of ischemia exists in anastomotic lines. It is important to know, however, in circumstances where blood flow may already be threatened, that attention to staple closure height with respect to bowel wall thickness may help preserve sutureline blood flow.

Inflexibility, a characteristic of all machines, is probably the most notable shortcoming of the stapler. Although staple closure height is adjustable in some instruments, the size and spacing of individual staples are not. A wider choice of diameters of the circular staplers, as well as size and spacing of staples, may enhance its use and reception by the surgical craftsman.

Acknowledgment

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DISCUSSION

DR. GEORGE H. A. CLOWES, JR. (Boston, Massachusetts): Dr. Chung, I would like to ask you a question as to whether we have any correlation between your observations on blood flow and the actual healing of suture lines in the gut of some animals other than the rat. The rat, unfortunately, is a poor animal to choose for something like this. Since rats have great resistance to infection, all you have to do is be socially clean for the rat to heal.

Secondly, most of us were brought up to believe that the serosa and its inflammatory reaction are of greatest importance in localization of leaks and infection at colonic suture lines. Dr. Ravitch's experiments some years ago in which he placed a rubber dam around a suture line and got a large percentage of breakdown showed the importance of the adjacent tissue to walling off infection at the suture lines.

Do I quote you correctly on that? Dr. Ravitch is going to respond.

DR. MARK M. RAVITCH (Pittsburgh, Pennsylvania): I believe one of the problems with almost any study of intestinal anastomosis is that nature is so forgiving and the *vis medicatrix naturae* is so beneficent that unless you do a bad job the bowel will heal very well.

I only need to remind you that we all have learned to apply our sutures lightly and tie them just tightly enough so they do not produce any compression. Yet, Edgar Poth of Galveston has done just the opposite. He puts the sutures through all thicknesses of bowel and says you must tie them tightly until you feel them cut through the muscle. He gets perfect results, and he can show by naked eye observation that whereas in a few minutes the lightly placed suture produces a little area of ischemia when edema comes, in contrast, his tight sutures loosen and there is no ischemia. This seems almost an anti-intellectual, anti-perfection argument, but the fact is that you can go home happy with the technique you have always used even though it disagrees with every one else's technique, and you get good results because nature is so forgiving.

DR. RAPHAEL S. CHUNG (Closing discussion): I thank the discussants for their comments.

Dr. Clowes, the ongoing experiments in our lab in which we tried to produce strictures by tight stapling is still ongoing. All I can say is it is difficult to produce bad results by tight stapling, as Dr. Ravitch has just pointed out.

I would also like to point out the enormous amount of clinical data indicating that over 90% of the time you can get away with closing the staple at a fixed gap of 2 mm, up and down the GI tract.

The significance of these laboratory data is that when the patient is at risk of developing anastomotic dehiscence because of pre-existing adverse conditions such as ischemia, the anastomoses should be sewn or stapled loosely rather than tightly.

Burn Wound Sepsis may be Promoted by a Failure of Local Antibacterial Host Defenses

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Little attention has been focused on the local burn wound environment, even though burn wound sepsis is a common cause of death in the burn victim. To characterize the effect of the local burn wound environment on neutrophil function and metabolism, the opsonic activity of blister fluid specimens against *Pseudomonas aeruginosa* was measured as was the effect of blister fluid on control neutrophil oxygen consumption using preopsonized zymosan and f-met-leu-phe (FMLP) as stimuli. Blister fluid did not support the killing of *P. aeruginosa* by normal neutrophils as well as normal serum. Additionally, blister fluid inhibited zymosan-stimulated, but not FMLP-stimulated, neutrophil oxygen consumption. The inhibitory effect of blister fluid on zymosan-stimulated oxygen consumption correlated with the extent of complement activation, measured as C3d or C3AI ($p < 0.01$). That blister fluid did not inhibit the FMLP-mediated respiratory burst supports the concept that the blister fluid inhibitory effect on the zymosan-mediated respiratory burst was mediated through the complement receptor. These findings that blister fluid can affect the bactericidal and metabolic activity of normal neutrophils support the concept that cellular function can be altered by the microenvironment in which the cells are bathed. This potential impairment of host defenses within the burn wound could predispose the burn victim to burn wound sepsis.

THE COMBINATION OF the loss of the skin barrier to bacteria and failure of both local and systemic immunity predisposes the burn patient to an increased risk of infection. Despite the fact that the burn wound is the most common portal of entry for invading bacteria, investigation of the effect of the burn wound environment on cellular components of the host's antibacterial defenses has been largely neglected. Previously, we documented that blister fluid will not support the phagocytosis or intracellular killing of *Pseudomonas aeruginosa* by control neutrophils collected from healthy volunteers as well as normal serum.[1,2] Furthermore, we found that the biologic effect of burn wound blister fluid was not limited to neutrophil bactericidal activity, but that blister fluid will also inhibit the blastogenic response of normal lymphocytes to the mitogen phytohemagglutinin (PHA).[3,4]

Although the exact mechanisms by which the blister fluid specimens affected neutrophil and lymphocyte function could not be fully determined from these previous studies, both the blister fluid opsinopathy and the lymphocyte inhibitory activity was associated with local consumption of C3 and the generation of complement breakdown products.[2,4] Since neutrophils have surface membrane complement receptors and evidence exists that C3 breakdown products can modulate neutrophil function through these receptors,[5-7] the current study was performed to correlate the levels of C3 and its stable metabolic breakdown product C3d, with the biologic effect of blister fluid on control neutrophil bactericidal and metabolic activity. The results of this study indicate that burn blister fluid has impaired opsonic activity for *P. aeruginosa,* and will depress the metabolic response of control neutrophils to zymosan. Furthermore, the suppressive effect of the blister fluid specimens on neutrophil metabolism correlated directly with the magnitude of complement activation. Further support for the role of complement breakdown products as mediators of impaired neutrophil function came from experiments documenting that blister fluid impaired complement-

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mediated, but not complement-independent, metabolic responses. Thus, the results of this study support the concept that a local failure of neutrophil function could occur in the burn wound and be mediated by local activation of humoral factors, such as complement. Thus, our results clearly show that local immunity is impaired after thermal injury, and that this impairment is due to more than just local destruction of the skin barrier. The failure of local immune defenses could predispose the burn victim to burn wound sepsis by allowing bacteria to colonize more easily and invade the burn eschar.

Patients, Materials, and Methods

Twenty-four patients admitted to the Louisiana State University (LSU) Burn Center in Shreveport form the basis for this study. The mean ± SD burn size was 35 ± 19% TBSA. The mean ± SD age was 31 ± 17 years, with 17 male and seven female patients. All patients were admitted directly to the Burn Unit within 6–12 hours of their injury. Resuscitation was based on the Parkland formula and was modified according to the clinical response of each patient. The burn wound area from which the blister fluid was obtained was not treated with topical antimicrobial agents. No prophylactic antibiotics were administered and none of the patients had sepsis at the time of the study.

Blister Fluid

Blister fluid was obtained by needle aspiration within 12–18 hours of thermal injury before the formation of any gel-like coagulation. Sterility was verified by culturing the blister fluid on blood agar plates for 24 hours. Each specimen was divided into aliquots and stored at −70 C until used.

Cell Preparation

A 15-mL sample of heparinized blood (10 U/mL) collected from healthy volunteers was mixed with 6% dextran and gravity sedimented at room temperature for 60–120 minutes. The leukocyte-rich supernatant was aspirated and washed three times in minimal essential medium, and viability was established by trypan blue exclusion.

Bacteria

P. aeruginosa strain 12-4-4 was obtained from Brooke Army Hospital, Fort Sam Houston, Texas. Bacteria were grown in tryptic soy broth for 18 hours at 37 C and then washed twice in phosphate-buffered saline (pH 7.2). The initial bacterial count was determined spectrophotometrically (620) and verified by pour plate assay.

Bactericidal Assay

The bacterial assay has been previously described.[2] Briefly, leukocytes at a final concentration of 5×10^6/mL were incubated with 10^6 CFU *P. aeruginosa* in minimal essential medium supplemented with either control serum or blister fluid (10% or 30%, v/v). The leukocyte–bacterial suspension was incubated at 37 C on a rotating shaker. Aliquotes of the suspension were pour plate assayed after 30 and 90 minutes of incubation to determine the total number of viable bacteria.

C3 Determination

Native C3 concentrations were measured by rocket immunoelectrophoresis in 1% agarose gel containing 0.01 M edetic acid and 0.8% (v/v) antiserum against native C3. Antiserum against native C3 was prepared from goat anti-human C3 (betalc/betala globulin) serum as described elsewhere.[8]

C3d Determination

Serum C3d levels were measured by rocket immunoelectrophoresis using a rabbit anti-human C3d serum. In this method, native C3 from edetic acid–plasma was precipated with 22% polyetheylene glycol (molecular weight 8000) and C3d was assayed in the supernatant. Medium electroendosmosis 1% agarose with 1.25% anti-C3d serum was used for immunoelectrophoresis procedures.[9]

C3 Activation Index

The C3 activation index (C3AI) expressing the C3d to native C3 ratio was computed as follows[10]:

$$\mathrm{C3AI} = \frac{\mathrm{C3d\ (mg/dL)} \times 100}{\mathrm{C3\ (mg/dL)}}$$

Hemolytic Complement Assay

Total hemolytic complement activity (CH100) was determined by the quantiplate technique.[2] In this system, the test serum is placed into wells cut in agarose plates containing standardized sheep erythrocytes sensitized with hemolysin. The degree of hemolysis is then determined by measuring the area of hemolysis surrounding the well.

Oxygen Consumption of Peripheral Blood Neutrophils

The assay of neutrophil oxygen consumption was performed polarographically using a Clark's electrode as described by Nakamura et al.[11] A suspension of 10^6 control neutrophils was placed in a Clark electrode chamber containing control medium, normal serum (20% or 80% v/v), or blister fluid (20% or 80% v/v). Five

TABLE 1. *Comparison of the Effect of Control Medium, Normal Serum, and Blister Fluid on Control Neutrophil Oxygen Consumption*

		Oxygen Consumption (nmol/O_2/min/10^6 cells)			
	N	Resting	Zymosan Stimulated	Total	SI
Media	10	0.15 ± 0.03 (a)*	0.51 ± 0.10 (a)	0.66 ± 0.12 (a, b)	4.6 ± 0.45 (a)
Blister fluid	24	0.22 ± 0.06 (b)	0.42 ± 0.14 (b)	0.64 ± 0.16 (a)	3.1 ± 0.89 (b)
Normal serum	9	0.18 ± 0.02 (c)	0.63 ± 0.22 (a)	0.81 ± 0.21 (b)	4.7 ± 1.34 (a)

* Groups that are statistically similar have the same letters in parentheses, whereas groups that are statistically different ($p < 0.05$) have different letters in parentheses. All values are expressed as mean ± SD. Blister fluid and normal serum specimens tested at 80% v/v. SI = stimulation index, which is computed by dividing total oxygen consumption by resting oxygen consumption.

microliters of 50 mM NaCN was added to inhibit cytochrome oxidase-dependent mitochondrial respiration. Baseline resting (unstimulated) neutrophil oxygen consumption was measured after a 6-minute adjustment period for temperature equilibrium. One minute later, zymosan preopsonized with normal serum (60 mg/mL) was added to the neutrophil suspension and the zymosan-stimulated increase (respiratory burst) in oxygen consumption was measured. Preopsonized zymosan was chosen as a probe to evaluate the complement-mediated oxidative response, since its phagocytosis is mediated through the C3b receptor. Since the synthetic peptide formly-met-leu-phe (FMLP) stimulates oxygen consumption through the FMLP receptor, which is independent of the complement receptor, it was chosen as a probe to evaluate the effect of blister fluid on the non-complement-mediated respiratory burst. FMLP was tested at a concentration of 10^{-7} molar.

Total oxygen consumption was computed by combining the values of the resting and stimulated oxygen consumption. The stimulation index (SI) was computed by dividing the stimulated oxygen consumption by the resting oxygen consumption.

Statistics

Results were expressed as mean ± SD or SEM. The statistical analyses were performed on an Apple II computer using the Stat pack program (Human Systems Dynamics, Northride, CA). Comparisons between groups were performed by Student's t-test for paired or unpaired data as appropriate. Correlations were analyzed by linear regression analysis. Values of $p < 0.05$ were considered statistically significant.

TABLE 2. *Comparison of Levels of Complement Components and Hemolytic Activity between Control Serum and Blister Fluid*

	N	C3B mg/dL*	C3d mg/dL	C3AI (%)	CH100
Serum	10	137 ± 25	2.2 ± .8	1.7 ± .7	43.5 ± 14.8
Blister fluid	34	69 ± 24	9.0 ± 4.6	14.6 ± 8.7	37.1 ± 16.2
t-test		$p < 0.001$	$p < 0.001$	$p < 0.001$	$p = 0.24$

* Results are expressed as mean ± SEM.

Results

When control neutrophils from healthy volunteers were incubated in blister fluid, several phenomena were observed. The level of resting (unstimulated) oxygen consumption of these cells suspended in blister fluid was increased compared with neutrophils suspended in media, whereas the zymosan-stimulated burst of oxygen consumption was lower in neutrophils suspended in blister fluid than those suspended in medium (Table 1). Since some of the changes between the neutrophils suspended in medium *versus* blister fluid could have been due to there being no protein source in the medium, the cells were also tested after suspension in pooled normal serum (80% v/v). Neutrophils suspended in normal serum had higher resting levels of oxygen consumption than cells suspended in medium ($p < 0.02$), but lower levels than those suspended in blister fluid. However, zymosan-stimulated oxygen consumption was higher in the neutrophils suspended in normal serum than neutrophils suspended in medium ($p = 0.14$) or blister fluid ($p < 0.05$) (Table 1). These results indicated that blister fluid effected both unstimulated and zymosan-stimulated oxygen consumption differently than medium or normal serum.

Next, we measured the complement levels (C3 and C3d) and hemolytic activity of these blister fluid specimens (CH100). As seen in Table 2, the levels of C3 were lower in the blister fluid specimens than in normal serum ($p < 0.01$). Additionally, the complement present in the blister fluid appeared to have been activated, since the level of C3d, the activation product of C3, was increased ($p < 0.01$), as was the C3 activation index (C3AI) ($p < 0.01$) (Table 2). Neither C3, C3d, C3AI, nor CH100 ($p > 0.24$) levels in the blister fluid correlated with the increase in resting neutrophil oxygen consumption. However, there was a correlation between C3 activation and depression of zymosan-stimulated oxygen consumption by the neutrophils, whether measured as C3AI ($R = -0.52$, $p < 0.01$), or C3d ($R = -0.57$, $p < 0.01$) (Fig. 1). Since there was no correlation between zymosan-stimulated oxygen consumption and the level of C3 ($p = 0.64$) or hemolytic activity ($p = 0.62$) of the blister fluid specimens, it appears that the decrease in zymosan-stimulated oxygen consumption of neutrophils suspended in blister fluid is associated more with complement activation than with the absolute levels of C3.

Previously, we documented that neutrophils suspended in blister fluid at 10% v/v do not ingest and kill *P. aeruginosa* as well as neutrophils suspended in normal serum. This defect in blister fluid biologic activity was primarily due to a deficiency of opsonic activity in the blister fluid, although the blister fluid impaired intracellular killing of phagocytized pseudomonads.[1] Since the concentration of blister fluid used in the bactericidal and metabolic assays were different and blister fluid concentration may be of biologic importance, we measured the effects of different blister fluid concentrations on bacterial killing and zymosan-stimulated oxygen consumption. Blister fluid at 10% or 30% v/v did not impair zymosan-stimulated oxygen consumption of control neutrophils compared with the same cells suspended in medium ($p < 0.14$), although these blister fluids at 80% v/v inhibited the zymosan-stimulated burst of oxygen consumption (Fig. 2). In contrast to the oxygen consumption assay, increasing the concentration of blister fluid from 10% v/v to 30% v/v or 80% v/v (data not shown) in the bactericidal assay restored neutrophil function to normal (Fig. 3). These results highlight the complexity of the relationship between complement and neutrophil function and illustrate that the same stimulus may influence various neutrophil functions differently.

To determine whether the inhibitory effect of blister fluid on the respiratory burst was limited to complement-mediated stimuli or effected both complement and noncomplement-mediated stimulated oxygen consumption, the effect of blister fluid on FMLP stimulation of neutrophils was measured. The levels of FMLP (10^{-7} molar) stimulated oxygen consumption of control neutrophils suspended in blister fluid was not different from neutrophils suspended in medium or serum (Fig. 4). These results indicate that the inhibitory effect of blister fluid on stimulated oxygen consumption may be mediated, at least in part, through the complement receptor.

Discussion

Burn wound sepsis occurs when bacteria colonizing the burn eschar successfully invade the viable subeschar tissue. In this situation, the humoral and cellular elements of the inflammatory response become a major host defense barrier.[12] That burn wound sepsis remains a frequent cause of morbidity and mortality in patients with major burns, despite the development of topical antimicrobial drugs, emphasizes that the patient's local antibacterial defenses have failed. Whether the failure of local immunity is due to the presence of burn-induced

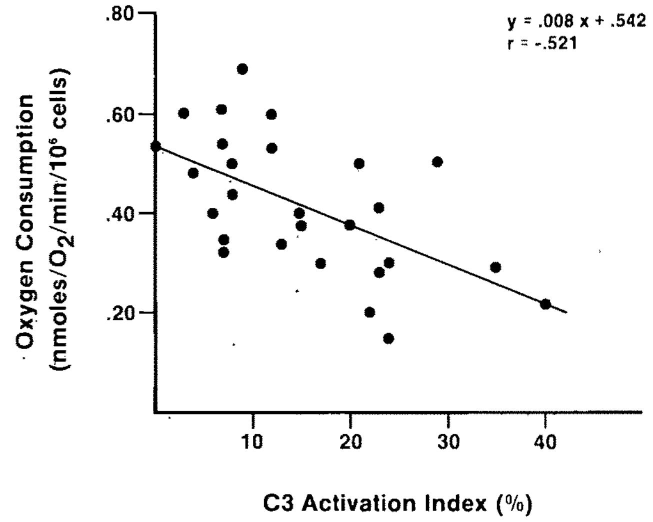

FIG. 1. There was a relationship between oxygen consumption (nmol/ O_2 min/10^6 cells) and complement activation measured as the C3 activation index ($R = -0.521$, $p < 0.01$).

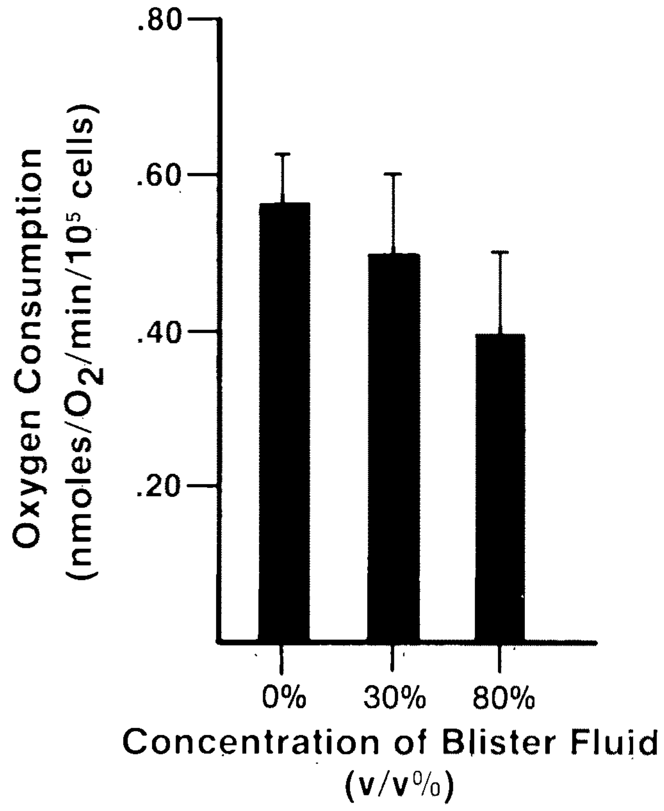

FIG. 2. The concentration (v/v%) of blister fluid ($N = 6$) in the oxygen consumption assay effected the amount of oxygen consumed by normal neutrophils stimulated by opsonized zymosan, since oxygen consumption in the presence of blister fluid at 80% v/v (respiratory burst) was lower than when the neutrophils were incubated at 10% or 30% v/v concentrations of blister fluid ($p < 0.03$).

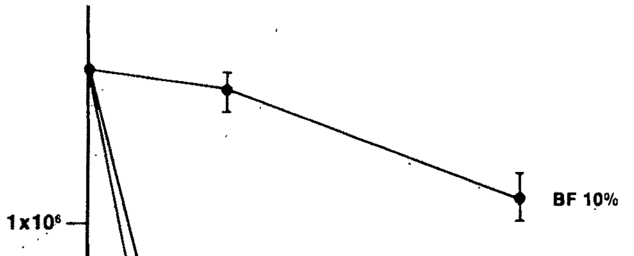

FIG. 3. Rate (mean ± SEM) of killing of *P. aeruginosa* by normal neutrophils incubated with blister fluid (N = 8) at 10% or 30% v/v concentration, or normal serum (N = 3) at 10% or 30% v/v.

suppressive factors, a local deficiency of normal host defense factors, or a combination of these or other factors, has not been extensively studied. For this reason, we have been interested in examining the effect of burn wound blister fluid on normal neutrophil and lymphocyte function and correlating its biologic activity with its chemical composition. In this way, it may be possible to understand how the local burn wound microenvironment may modulate the cellular arm of the host's antibacterial defense system. In previous work we documented that blister fluid will not support the opsoninophagocytosis or intracellular killing of *P. aeruginosa* by control neutrophils, although *Staphylococcus aureus* are killed normally,[1] and that a subset of the blister fluid samples inhibits mitogen-stimulated lymphocyte blastogenesis.[3] Further study of these blister fluid specimens suggested that the failure of the blister fluid to support the ingestion of pseudomonads by normal neutrophils was due to the local activation and consumption of complement in the burn wound and was not primarily due to the presence of inhibitory factors.[2] In contrast, blister fluid directly suppressed the response of normal lymphocytes to the mitogen PHA and the lymphocyte suppressive factor(s) appeared to be related to C3 metabolic products.[4] Thus, although the biologic activity of blister fluid appears to be different for different cell populations, in both instances the cellular changes were associated with complement activation.

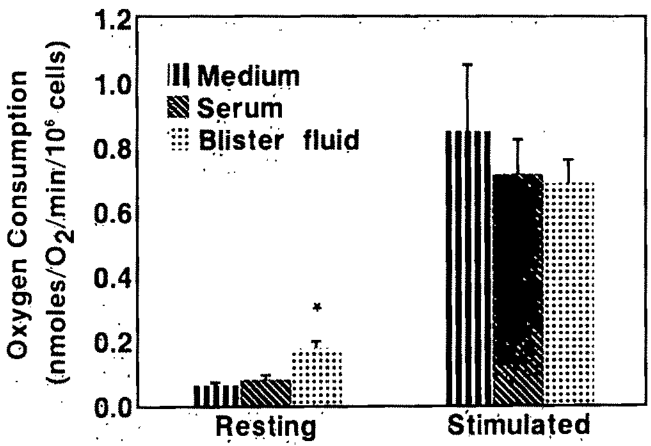

FIG. 4. No difference was found between the effect of control medium, normal serum (80% v/v), and blister fluid (80% v/v) on the FMLP-mediated (10^{-7} M) respiratory burst.

The current studies were performed to further characterize the biologic effect of blister fluid on normal neutrophil bactericidal activity and metabolism. Since bacterial phagocytosis and killing are accompanied by a dramatic rise in nonmitochondrial respiration, which correlates with the zymosan-stimulated oxygen (respiratory) burst,[13] and blister fluid did not support the ingestion and killing of *P. aeruginosa,* we were especially interested in measuring the effect of blister fluid on control neutrophil oxygen consumption. We found that blister fluid directly inhibited the respiratory burst of zymosan-stimulated neutrophils, and the degree of inhibition of the neutrophil's metabolic response to zymosan correlated with the degree of complement activation, measured as the level of the C3 metabolic product C3d ($p < 0.01$). The blister fluid effect on neutrophil bactericidal activity was maximal at 10% v/v, whereas its effect on oxygen consumption was maximal at 80% v/v concentration. The blister fluid-mediated effect on the respiratory burst appeared to be specific to complement-mediated stimuli, since blister fluid did not reduce the respiratory burst of neutrophils exposed to FMLP, which is a noncomplement-mediated stimulus. Thus, the blister fluid specimens appear to have disparate effects on neutrophil bactericidal activity and neutrophil metabolism, which is concentration and stimulus dependent.

There are several theoretical explanations for these findings. It is known that neutrophil receptors modulate the cell's ability to respond to stimuli by changing the affinity of the receptor according to the cell's environment.[14] For example, from studies using the chemoattractant FMLP, it is clear that as the concentration of FMLP increased, the neutrophils adapt by decreasing receptor affinity for this chemoattractant. This results in the neutrophil becoming chemotactically paralyzed (deactivated) when exposed to a high concentration of a chemoattractant,[15] while at the same time, neutrophil degranulation is increased. Thus, chemoattractants, such as C5a and FMLP, at concentrations that cause chemotactic deactivation, also promote neutrophil degranulation. In essence, these changes in receptor affinity potentially allow the cell to adapt its response according to its microenvironment. Since the respiratory burst is associated with a low receptor affinity state,[14,16] the changes we observed with zymosan could be due to alterations in complement receptor affinity induced by the blister fluid. That is, the blister fluid at an 80% v/v concentration could stimulate the basal neutrophil metabolic rate, while simultaneously decreasing the affinity of the cell for subsequent complement-mediated stimuli. Thus, when zymosan is added, the cells would be relatively refractory to this second complement-mediated stimulus. The scenario of increased basal oxygen consumption and decreased stimulated oxygen consumption of neutrophils suspended in blister fluid could, therefore, be related to neutrophil deactivation or receptor-mediated down regulation. This same pattern of increased basal and decreased stimulated oxygen consumption could result from a blister fluid-mediated increase in basal energy utilization resulting in decreased energy stores (metabolic exhaustion). This possibility is unlikely since the cells responded normally to FMLP.

Another possible explanation for the different effects of blister fluid on bactericidal activity *versus* zymosan-mediated oxygen consumption is that the blister fluid in some fashion dissociates oxygen consumption from bactericidal activity.[17] This dissociation could be related to the uncoupling of oxygen consumption from glucose utilization resulting from different sensitivities of these pathways to modulation by factors present in the blister fluid or because the neutrophil uses nonoxygen-dependent pathways for microbicidal activity.[18] Lastly, the blister fluid may contain other selective inhibitors of oxygen consumption that only become apparent when zymosan is used as a probe and the blister fluid is present at high enough concentrations. It is likely that our findings are not the result of a single mechanism, but may be the summation of several of the above described mechanisms.

Since both the phagocytosis of *P. aeruginosa* and the zymosan-mediated respiratory burst are complement-mediated phenomenon and evidence has accumulated that various fragments of C3 can modulate neutrophil, macrophage, and lymphocyte function,[5-7,19] we measured native C3, C3d, and C3AI concentrations in the blister fluid specimens. The levels of C3 were lower, whereas the levels of the C3 metabolic product C3d and the C3AI were higher in the blister fluid specimens than in control serum, indicating that native C3 in blister fluid has been activated (Table 2). No relationship between absolute complement levels (C3 and C3d) or complement activity (C3AI or CH100) and basal oxygen consumption was found, indicating that the blister fluid-mediated increase in basal neutrophil oxygen consumption is not associated with increased C3 activation. However, there was an inverse correlation between C3 activation, whether measured as C3d or C3AI, and zymosan-stimulated oxygen consumption (Fig. 1). The nature of the specific complement activation product that modulates the impaired respiratory burst of control neutrophils to zymosan is not known, but based on the work of Ogle et al. it may be fluid phase C3b.[5]

Although the association between complement activation and inhibition of the zymosan-stimulated respiratory burst is statistically significant, the degree of correlation ($R = 0.52$) does not account for the entire inhibitory effect of the blister fluid on the respiratory burst. Therefore, other factor(s), such as the prostaglandins, serotonin, histamine, or interleukin-1,[20] all of which have been found in blister fluid, may also modulate the zymosan-mediated respiratory burst.

The relationship between the complement system and neutrophil bactericidal and metabolic responses are of great potential clinical importance, since *in vivo* bacterial phagocytosis and killing by phagocytes is mediated to a large extent by the C3 receptor.[21] Our findings that blister fluid can affect the bactericidal and metabolic activity of normal neutrophils emphasizes that cellular function can be altered by the microenvironment in which the cells are bathed. The findings that blister fluid impairs normal neutrophil bactericidal activity and metabolism is consistant with the work of Alexander and associates, who have shown that a consumptive opsinopathy occurs in the serum of burn patients.[22] Furthermore, Cohen et al.[23] and Polk et al.[24] have documented an opsonic failure of diluted serum in trauma victims and stressed or debilitated patients, whereas Lanser et al. have found that the serum of trauma victims contain an inhibitor of neutrophil metabolism.[25] Thus, our findings that burn wound blister fluid can impair neutrophil function correlates well with the systemic effects documented by other investigators in the serum of victims of thermal or mechanical trauma. Based on the results of these experiments and our previous work, we believe that blister fluid by altering normal neutrophil function could promote the uncontrolled local growth of microorganisms in the burn wound. Furthermore, failure of local defenses could be the first step in the development of burn wound sepsis. However, the ultimate clinical result of the failure of local antibacterial defenses would depend on additional factors, including the patient's overall immune state.

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DISCUSSION

DR. P. WILLIAM CURRERI (Mobile, Alabama): Dr. Deitch and his colleagues have previously reported investigations that have suggested that there are local factors in blister fluid which have profound effects on phagocytosis and intracellular killing by control neutrophils collected from healthy volunteers.

In this presentation they examine opsonic activity and cellular metabolism as reflected by oxygen consumption to test for a relationship between complement activation and neutrophil oxygen consumption, the latter of which is a known important process required for intracellular killing of bacteria.

Their data indicate that there is a severe decrease in zymosan-stimulated oxygen consumption by neutrophils incubated in blister fluid compared with such cells incubated in media or normal serum. Furthermore, the blister fluid appeared to have been activated since there was a significant increase in C3d and the activation index.

At best a modest negative correlation was demonstrated between C3 activation and the depression of zymosan-stimulated oxygen consumption by the neutrophils.

The authors have suggested several theoretical explanations for these findings including down regulation of the neutrophil as a result of exposure to high levels of activated complement, the disassociation of oxygen consumption from bacteriocidal activity, and the presence of other selective inhibitors of oxygen consumption that only become apparent in the presence of blister fluid when zymosan stimulation is used as a metabolic probe.

Because of the relatively low correlation between complement activation and oxygen consumption observed in these studies (as illustrated by an R value of only 0.5–0.6), the latter two explanations become more attractive.

The data presented today did not strongly suggest a cause and effect between complement activation and the subsequently observed decreased stimulated oxygen burst as a single mechanism associated with decreased neutrophil inhibitory function. Nevertheless, these observations are intriguing and will certainly stimulate these and other investigators to search for other selective inhibitors of oxygen consumption within burn blister fluid and to further delineate the role of activation of complement as a direct cause of neutrophil down regulation.

I would like to direct a number of specific questions to the authors.

First, do the authors believe that their observations can be extended to third degree burn where blister formation is not prominent? Such burns are relatively dry, and therefore, might present a different local wound environment.

Secondly, staphylococcal bacterial infection of the second degree burn wound occurs at least as commonly as Pseudomonas infection of the second degree burn wound. If the proposed mechanism of down regulation of neutrophil activity is an important component in local immunity, how do the authors explain the common finding of staphylococcal colonization of second degree burns? Finally, have the authors tested the effect of blister fluid on neutrophils collected from burn patients? Such studies might elucidate the presence of systemic circulating factors that serve to block complement receptors on the neutrophil, which are independent of the local environment created by the blister fluid.

DR. JOHN A. MANNICK (Boston, Massachusetts): As usual I am impressed by the originality of Dr. Deitch's research, and I am convinced of the accuracy of his data.

I am slightly less convinced by his conclusions. I believe that it is apparent that something in blister fluid is inhibiting neutrophil activation, at least by zymosan. Is it possible that what is happening here has nothing to do with complement? For example, can we attribute all of this to an increase in proteolytic enzymes in the blister fluid? Certainly most inflammatory exudates including peritoneal fluid have enough proteolytic enzymes to digest off complement receptors from neutrophils. Could this be what is happening?

I believe this sort of question could be answered if Dr. Deitch has any data about the expression of complement receptors on the neutrophils in his experiments. Since technology is currently available to allow these experiments to be done, that would be one way of settling the issue.

I am more disturbed by the question of whether or not the blister fluid and its effects on neutrophil activation actually has anything to do with the invasion of the burn wound by bacteria. I would have believed that perhaps a more important gauge of the host defense against bacteria would be the function of the neutrophils in the capillaries at the edge of the burn wound. Dr. Francis Moore, Jr. at our hospital has shown convincingly that the circulating neutrophils in patients with burns of equivalent size to those studied by Dr. Deitch are very activated as they circulate *in vivo* as reflected by severely increased representation of complement receptors on the cell surface, and we have been unable to show that these cells lack ability to kill bacteria when studied *in vitro*. Therefore, I believe that Dr. Deitch has presented us with some interesting experimental findings, but I am not sure whether or not they have relevance to the invasion of the burn wound by pathogenic bacteria.

DR. BASIL A. PRUITT, JR. (Fort Sam Houston, Texas): I, too, would like to compliment Dr. Deitch and his coauthors on another in their interesting series of studies dissecting the factors responsible for the increased susceptibility to infection after injury, and to thank him for providing me with the manuscript well in advance of the meeting.

I would like to preface my further comments with a semantic niggle. That is, burn wound sepsis refers to the clinical constellation of organ failure that is elicited by hematogenous dissemination of microorganisms or their metabolic products from a site of invasive burn wound infection. Surely Dr. Deitch means burn wound invasion rather than burn wound sepsis.

The data presented suggest that burn wound blister fluid impairs complement-mediated phagocytosis, and inhibits complement-mediated neutrophil oxygen production but does not affect complement-independent oxygen production by neutrophils stimulated by FMLP. These findings are interpreted as indicating that blister fluid impairs neutrophil function in the wound, and thereby permits local microbial growth. Since blisters are characteristic of second degree burns, one might conclude that such wounds are particularly susceptible to infection, but clinically they are much more resistant to infection than third degree burns where there are no blisters, and I would like the authors to explain that paradox.

To assist us in evaluating his findings, Dr. Deitch will need to supply us with a few more experimental details. First, were differential counts performed on the neutrophil preparations to ensure a comparable cell population in each test system? Second, since oxygen production of normal neutrophils should increase 10–20-fold when stimulated, how do you explain the modest threefold increase you observed? Third, how confident are you that variable aggregation and adherence of polymorphonuclear leukocytes to the electrode membrane did not affect your measurements? Fourth, since endotoxin can influence PMN function, did you measure endotoxin levels in the blister fluid samples to assess whether they were responsible for the observed changes?

I also ask what you consider the clinical implication of these data to be? Since many bacteria have amino acid sequences analogous to FMLP and responsiveness to that material was maintained, was polymorphonuclear chemotaxis in the wound actually decreased? Lastly, I ask whether this study leads you to recommend the immediate debridement of all bullae and blisters from second degree burn wounds?

DR. ANDREW M. MUNSTER (Baltimore, Maryland): I thank Dr. Deitch for not providing me with a copy of the manuscript because it makes you think on your feet quickly.

I have a few minor questions. There is another receptor on the neutrophil, and that is the FC receptor, and I am not altogether convinced from his data that he is showing active inhibition of function rather than deficiency disease. Therefore my question is: did he measure IgG levels and IgM levels, particularly IgG levels in the blister fluid?

This is particularly important because a number of groups currently are looking at the effect of the intravenous IgG preparations on protection from burn wound sepsis.

My second question is: where did the Pseudomonas come from that these neutrophils were tested against because we have recent evidence in our laboratory that shelf Pseudomonas is not handled the same way by neutrophils as a clinical isolate from the same patient. Finally, I would like to echo the other comments inasmuch as I do not known what blister fluid is. I do not know if it can be representative of local wound environment or not, particularly in light of previous work from Galveston, performed 15 years ago, which show that the movement of the various components of IgG and IgM differ in the burn area inwards, outwards, and into the cell. Therefore, what do you think the blister fluid means?

DR. J. WESLEY ALEXANDER (Cincinnati, Ohio): I also compliment Dr. Deitch on his clear presentation and continued contributions to this particular area and emphasize that he is trying to look at the potential mechanisms of altered host resistance caused by blister fluid as it leaks out into the wound.

(Slide) There is great interest regarding complement activation in surgical diseases, and I want to point out that most of the conditions that are associated with intense and chronic complement activation are associated with an increase in the incidence of bacterial infections.

There has been particular interest in the breakdown products of C3 in this phenomenon. As you will recall, C3 is cleaved into C3a and C3b. C3b is the larger fragment of these, and it usually attaches very soon to a susceptible membrane if it is to participate in phagocytosis.

If it does not set down on that membrane within a few seconds, it undergoes a confirmational change in its protein structure and is unable to attach to those membranes and is called fluid phase C3b.

Fluid phase C3b is broken down to C3bi and further to C3c and C3d. Dr. Deitch used one of these in his investigations.

C3b is a particularly interesting fragment because it can induce phagocytosis when bound, but it inhibits phagocytosis and the killing of bacteria when it is in the fluid phase. Additionally, it can directly interact with the membranes of phagocytic cells to stimulate production of active oxygen species and to induce the release of a variety of enzymes and degranulation from the neutrophils.

When injected intradermally with bacteria into the backs of guinea pigs, it can increase lesion size, using the Burke model, indicating that there is an increase in the infectability, and when injected intraperitoneally with bacteria it can inhibit the clearance of bacteria from the peritoneal cavity.

Therefore, C3b may have an important effect by interfering with phagocytic function not only by depletion of the active C3b that sits down on the membrane and increases phagocytosis, but also by serving as an inhibitor substance, which inhibits the subsequent function of neutrophils.

I must say that we have a different outbred population in Cincinnati than Dr. Mannick does in Boston. We do see neutrophil defects in burned patients as a variety of other subjects.

I ask Dr. Deitch several questions related to this. One, have you fractionated the blister fluid to try to identify specific inhibitors related to the complement system? Second, have you dialyzed blister fluid to look for inhibitors because there are those related to the leukotrienes in prostaglandins, which also have an inhibitory effect on neutrophil function? Finally, have you looked for any suppressive peptides such as those that have been described by Dr. Mannick and Dr. Ozkin?

Dr. Stanley M. Levenson (Bronx, New York): I would like to ask Dr. Deitch one question. As I understand it you interpret the relative differences in the C3 and C3D levels in the burn blister fluid compared with those in the serum as reflecting activation of complement in the burned tissue and/or in the blister fluid itself. Would an alternate interpretation be that the differences reflect differences in the rates at which these molecules cross the heat-damaged capillary walls because of the differences in their molecular weights?

Dr. George H. A. Clowes, Jr. (Boston, Massachusetts): I would like to add one question. We have recently studied in some detail the presence of interleukin I and its products, and we know that this stimulates the growth of granulation tissue and other defensive functions, and also can be an inhibitor.

It seems to me that you have heard several discussants, all of whom have suggested different things in the fluid. It is going to be your problem to sort it out now.

Dr. Edwin A. Deitch (Closing discussion): I thank all the discussants for their questions. I believe the best way of approaching these questions may be by summarizing some of the questions so that I have adequate time to address them all.

First, let me describe what blister fluid is and answer some of the questions about what could be in it.

We have published previously some work on cross-electrophoresis measuring 21 proteins in blister fluid as well as similar levels in serum immediately after injury. What we found was that the blister fluid was a filtrate of the plasma, and as Dr. Levenson suggested, whatever proteins are in the plasma come across into the blister fluid. With the exception of the C3 breakdown products, the concentration of proteins in blister fluid reflects their concentration in serum. The level of C3d in the blister fluid is about five times the level in the plasma; therefore, it appears as if proteins are going across and there is a linear relation between the log molecular weight of the protein and its concentration in blister fluid with the exception of C3 breakdown products.

My best explanation for these findings is that C3d is being produced locally due to activation of complement in the burn wound.

The question about interleukin I is very interesting. Last year I did some work in collaboration with Dr. Tom Kupffer and Dr. Chip Baker from Yale, and we presented data showing that blister fluid has high levels of interleukin I-like activity, which may be due to epidermal thymocyte activating factor (ETAF). In fact, the levels of IL-1 activity in blister fluid were approximately 100 U/mL when it was quantitated. Therefore, the blister fluid does contain high levels of interleukin I activity and thus could be at least a source for these factors that circulate throughout the body.

I believe Dr. Alexander has said it very well. That is, what I am trying to do with these experiments is to determine what is happening at the level of the local wound. We all know that bacteria have to cross mechanical barriers to gain access to the body. Whenever that barrier is weakened, whether by the presence of a Foley catheter in the bladder, an endotracheal tube in the lung, an IV in a vein, or damaged skin, the net result is that bacteria may cross more easily.

The first defense that is called into play once bacteria have crossed these mechanical barriers and invaded viable tissue is the inflammatory response. Humoral factors that are associated with the inflammatory response cooperate with locally recruited neutrophils to increase bactericidal capabilities of these phagocytic cells.

What we are looking at with blister fluid is: does the humoral factors that are present in the burn wound affect the biological activity of normal neutrophils? What we have found is that blister fluid effects neutrophil function differently than normal serum or neutral media.

As far as how blister fluid is mediating the changes in neutrophil function, I do not believe that we can say with certainty that all of the affects of blister fluid on neutrophil function is being mediated through complement factors. However, there is a statistically significant inverse correlation between the level of complement activation, measured as C3d or the C3AI and neutrophil metabolism.

As Dr. Alexander mentioned, we also have found early on after a burn injury that neutrophil function is impaired, especially chemotaxis. Therefore, I believe that local immunity must be severely impaired, since the neutrophils reaching the burn wound may not be normal and the humoral microenvironment in which the PMMs must function is not optimal.

I would like to address next what I believe is one of the most difficult questions to answer. That is, do our results with second degree burns apply to third degree burns. This is a difficult question to answer with certainty, but I believe the answer is yes. Drs. Baxter and Dobke have collected wound fluid from patients with third degree burns and have found that this fluid is biologically similar to blister fluid.

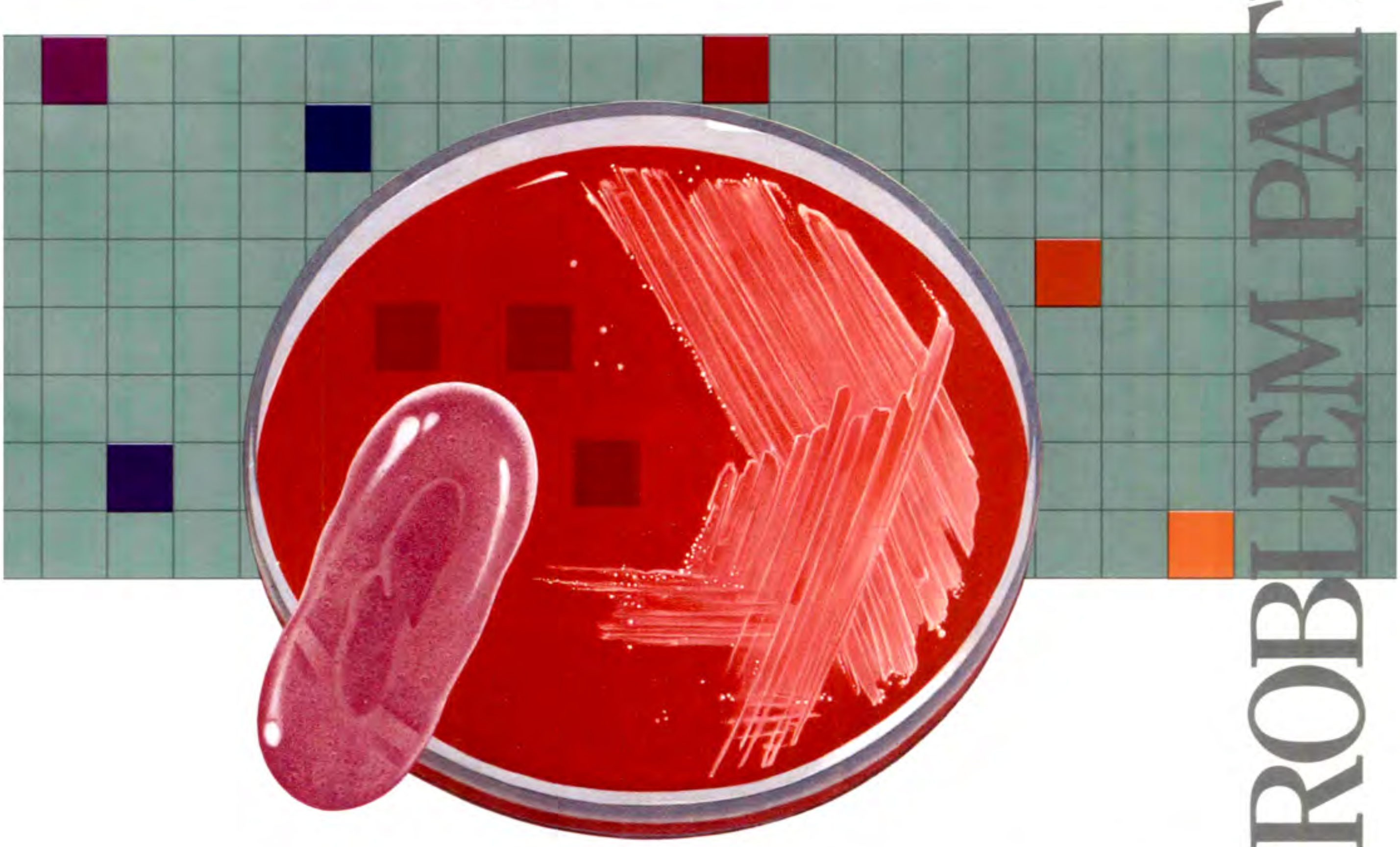
I believe the study of blister fluid is cleaner than wound fluid, since blister fluid is sterile and does not contain cellular debris. We have tested for endotoxin, and blister fluid is negative. Also, I believe that any biological fluid that reaches the burn wound will be activated, since this fluid will be exposed to denatured collagen and damaged tissue. In this regard, there is no difference between second and third degree burns, since in both instances collagen is exposed, and exposed collagen can activate both the coagulation cascade and the complement system.

To answer some technical questions, I can answer that we checked the neutrophils' viability. We also checked them to make sure that they were highly pure. Dr. Pruitt accused us of having puny neutrophils. Based on our previous work, as well as the work of others, the stimulation index that we find with our neutrophils is similar to what is reported around the country. The stimulation index, depending on the stimulant, zymosan or FMLP, is generally between 3 and 5.

Thank you for your attention.

When B fragilis is the Threatening Organism

PROBLEM PATHOGENS



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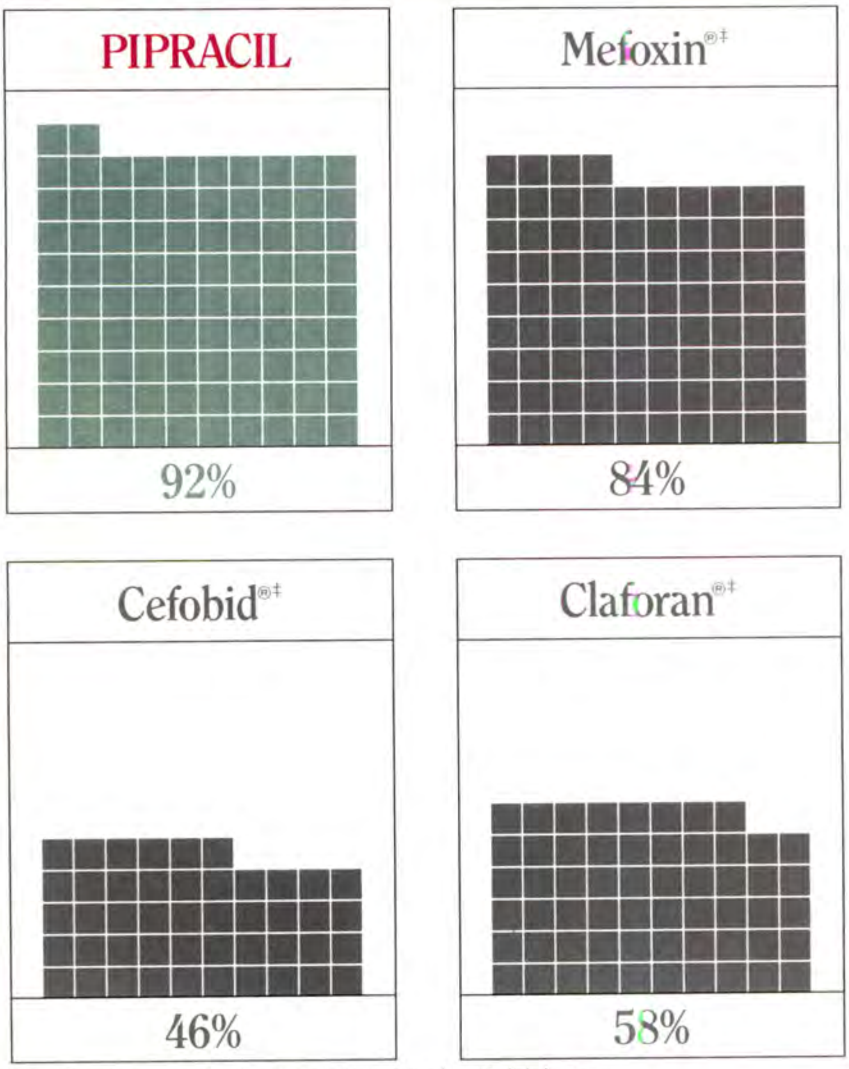
PIPRACIL: More Active Against *Bacteroides fragilis* Than Cephalosporins[1]

88%-92% Susceptibility *In Vitro** *v B fragilis* Over a Three-Year Period†

Results of nationwide susceptibility study of 555 strains obtained from eight US centers[1]



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*Although a useful guide, *in vitro* activity does not necessarily correlate with clinical response.

†1981, 1982, 1983.

‡Mefoxin (cefoxitin) is a registered trademark of Merck Sharp & Dohme. Claforan (cefotaxime) is a registered trademark of Hoechst-Roussel. Cefobid (cefoperazone) is a registered trademark of Roerig.

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A Brief Summary
Consult package insert for full prescribing information.

INDICATIONS AND USAGE: Therapeutic. PIPRACIL is indicated for the treatment of the following serious infections caused by susceptible strains of the designated organisms: Intra-abdominal, urinary tract, gynecologic, lower respiratory tract, skin and skin structure, bone and joint, gonococcal infections, and septicemia.

Prophylaxis. PIPRACIL is also indicated for prophylactic use in surgery including intra-abdominal (gastrointestinal and biliary) procedures, vaginal hysterectomy, and cesarean section.

CONTRAINDICATIONS: A history of allergic reactions to any of the penicillins and/or cephalosporins.

WARNINGS: Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients receiving therapy with penicillins. These reactions are more apt to occur in persons with a history of sensitivity to multiple allergens.

There have been reports of patients with a history of penicillin hypersensitivity who have experienced severe hypersensitivity reactions when treated with a cephalosporin. Before initiating therapy with PIPRACIL® sterile piperacillin sodium, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, and other allergens. If an allergic reaction occurs during therapy with PIPRACIL, the antibiotic should be discontinued. The usual agents (antihistamines, pressor amines, and corticosteroids) should be readily available. SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN AND INTRAVENOUS CORTICOSTEROIDS AND AIRWAY MANAGEMENT INCLUDING INTUBATION SHOULD ALSO BE ADMINISTERED AS NECESSARY.

PRECAUTIONS: General. While PIPRACIL possesses the characteristic low toxicity of the penicillin group of antibiotics, periodic assessment of organ system functions including renal, hepatic, and hematopoietic during prolonged therapy is advisable. Bleeding manifestations have occurred in some patients receiving β-lactam antibiotics including piperacillin. These reactions have sometimes been associated with abnormalities of coagulation tests such as clotting time, platelet aggregation, and prothrombin time and are more likely to occur in patients with renal failure. If bleeding manifestations occur, the antibiotic should be discontinued and appropriate therapy instituted.

The possibility of the emergence of resistant organisms which might cause superinfections should be kept in mind, particularly during prolonged treatment. If this occurs, appropriate measures should be taken.

As with other penicillins, patients may experience neuromuscular excitability or convulsions if higher than recommended doses are given intravenously.

PIPRACIL is a monosodium compound containing 1.85 milliequivalents of Na^+ per gram. This should be considered when treating patients requiring restricted salt intake. Periodic electrolyte determinations should be made in patients with low potassium reserves, and the possibility of hypokalemia should be kept in mind with patients who have potentially low potassium reserves and who are receiving cytotoxic therapy or diuretics.

Antimicrobials used in high doses for short periods to treat gonorrhea may mask or delay the symptoms of incubating syphilis. Therefore, prior to treatment, patients with gonorrhea should also be evaluated for syphilis. Specimens for darkfield examination should be obtained from patients with any suspected primary lesion and serologic tests should be performed. In all cases where concomitant syphilis is suspected, monthly serological tests should be made for a minimum of four months.

As with other semisynthetic penicillins, PIPRACIL therapy has been associated with an increased incidence of fever and rash in cystic fibrosis patients.

Drug Interactions. The mixing of PIPRACIL with an aminoglycoside *in vitro* can result in substantial inactivation of the aminoglycosides.

Pregnancy—Pregnancy Category B. Although reproduction studies in mice and rats performed at doses up to four times the human dose have shown no evidence of impaired fertility or harm to the fetus, safety of PIPRACIL use in pregnant women has not been determined by adequate and well-controlled studies. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. It has been found to cross the placenta in rats.

Nursing Mothers. Caution should be exercised when PIPRACIL is administered to nursing mothers. It is excreted in low concentrations in milk.

Pediatric Use. Dosages for children under the age of 12 have not been established. The safety of PIPRACIL in neonates is not known. In dog neonates dilated renal tubules and peritubular hyalinization occurred following administration of PIPRACIL.

ADVERSE EFFECTS: PIPRACIL is generally well tolerated. The most common adverse reactions have been local in nature, following intravenous or intramuscular injection. The following adverse reactions may occur:

Local Reactions. Thrombophlebitis (4%), pain, erythema, and/or induration at the injection site (2%) and, less frequently, ecchymosis, deep vein thrombosis, hematomas.

Gastrointestinal. Diarrhea and loose stools (2%); less frequently, vomiting, nausea, increases in liver enzymes (LDH, SGOT, SGPT), hyperbilirubinemia, cholestatic hepatitis, bloody diarrhea, and, rarely, pseudomembranous colitis.

Hypersensitivity Reactions. Anaphylactoid Reactions (see WARNINGS). Rash (1%); less frequently, pruritus, vesicular eruptions, positive Coombs tests.

Renal. Elevations of creatinine or BUN and, rarely, interstitial nephritis.

Central Nervous System. Headache, dizziness, fatigue.

Hemic and Lymphatic. Reversible leukopenia, neutropenia, thrombocytopenia, and/or eosinophilia have been reported. As with other β-lactam antibiotics, reversible leukopenia (neutropenia) is more apt to occur in patients receiving prolonged therapy at high dosages or in association with drugs known to cause this reaction.

Serum Electrolytes. Individuals with liver disease, or individuals receiving cytotoxic therapy or diuretics, were reported rarely to demonstrate a decrease in serum potassium concentrations with high doses of piperacillin.

Skeletal. Rarely, prolonged muscle relaxation.

Other. Superinfection, including candidiasis
Hemorrhagic manifestations.

Rev. 5/86

References:

1. Tally FP, Cuchural GJ Jr, Jacobus NV, et al: Nationwide study of the susceptibility of the *Bacteroides fragilis* group in the United States. *Antimicrob Agents Chemother* 1985;28:675-677.

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An Access-oriented Negotiated Fee Schedule

The Caterpillar Experience

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This paper describes the system used by Caterpillar Corporation (CAT) in Peoria, Illinois, to reimburse surgeons. The CAT system assures access for Caterpillar employees and their families to a selection of qualified surgeons, while achieving cost savings through improvements in processing of surgical claims and negotiation of selected fees. CPT-4 codes are recoded for greater accuracy, when indicated, surgical services that have been incorrectly unbundled are rebundled, and the appropriateness of surgical assistant charges is reviewed. A "degree of difficulty" relative value scale (DODRVS) of surgical services is periodically revised as technology changes. The DODRVS multiplied by a regional factor, determined by local market research, establishes the fee that CAT will pay the surgeon. Balance billing is permitted if the patient (1) is informed in advance by the surgeon that the fee will be higher than CAT will pay, and (2) knows that the service can be obtained from other local surgeons who will accept the CAT fee. The goal of the CAT method of surgeon reimbursement is to gain physician support for an access-oriented, market-driven negotiated fee schedule. Compared with a resource-based relative value scale (RBRVS) methodology, the CAT system is not formula-driven and depends on physician acceptance.

FOR MORE THAN 25 years, physicians have benefited from a generous fee-for-service system of payment. However, between 1965 and 1985, national expenditures for physicians' services have increased almost tenfold, from $8.5 billion in 1965 to $82.8 billion in 1985.[1] As a result, several possible physician payment reforms are being considered. Prospective payment by diagnostic-related groups (DRGs), put in place to control Medicare hospital expenditures, is a fact of life for hospitals. Medicare and Medicaid are now pushing for changes in the way they pay physicians. Managed care programs are negotiating discounts from all types of health care providers.

Reform activity can be identified on many fronts: (1) Congress has frozen Medicare fees, effective June 1984 through January 1987. Congress' intent is now to shift the burden of effectively constraining the growth of Medicare Part B costs to providers rather than Medicare beneficiaries. (2) The Physician Payment Review Commission, created by Congress, has issued a recent major report, outlining ways that physicians could be reimbursed under Medicare in the future.[2] (3) In fall 1985, the Health Care Financing Administration (HCFA) contracted with Harvard University to conduct a 30-month study of resource-based relative value scales (RBRVS) for physician services.[3] This system is being developed under the direction of William Hsiao, Ph.D., Harvard School of Public Health. The American Medical Association is a subcontractor on the study for HCFA. The study is scheduled to be completed in July 1988. (4) The Massachusetts Rate Setting Commission is revising its Medicaid fee schedule, based on the RBRVS, for planned application in mid-1987. (5) The Massachusetts Insurance Commissioner asked Blue Shield to consider reforms in physician payment, with an emphasis on developing an RBRVS, as a condition of his approving a Blue Shield rate increase in 1987. (6) Congressional hearings on physician fee schedules continue, and congressionally sponsored studies of physician fees have recently been published.[4,5]

Within the administration in Washington, proponents of physician fee reform are calling for an expanded use of capitation in the long term, or some form of physician DRGs.[6] But these changes are not imminent. During the next several years, fee payment modifications will be based in fee-for-service recalculations. If the revised physician fee schedules achieve acceptable levels

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Submitted for publication: April 24, 1987.

TABLE 1. *Medicare Prevailing Fees* ($, 1984)*

State	CABG	Appendectomy	Cataract
New York	6000	1134	1547
Michigan	3100	399	825
Rhode Island	2587	516	928

* The charges indicated are for specialists and for the large urban areas within the states listed.

From the U.S. Department of Health and Human Services, Health Care Financing Administration. Medicare Directory of Prevailing Charges 1984. Washington DC: U.S. Government Printing Office, 1984.

of patient access and physician support, they will be part of the blueprint for future health care delivery in both private and public arenas.

Background

Medicare's "customary, prevailing, and reasonable" (CPR) payment system is, by general consensus, unsatisfactory in today's competitive market in health services. There are many problems associated with CPR. It tends to be inflationary and slow to respond to alternatives in technology and changes in both availability of physicians and need for services. Some charges appear excessive to most observers, even taking into account geographic cost-of-living variations and other variables. For example, under Medicare, the cost of a triple vessel CABG (coronary artery bypass graft) in New York in 1984 was $5500. The cost of this same procedure in Michigan was $3100 and $2587 in Rhode Island (Table 1).

Similar variations are found in fees from the private sector. For example, unexplained fee variations exist in managed health care models such as independent practice associations (IPAs). Hip replacement at three different IPAs in the eastern part of the country ranged from $2808 to $4274 (see Table 2).

Noting these wide discrepancies, the federal government and a number of large private purchasers of health services have turned their attention to the ways physicians are compensated for the care they provide. Fundamental changes in the methodology of physician reimbursement are being discussed. Serious consideration is being given to systems that would pay physicians by capitation or by including the physician payment with the hospital DRG payment. However, both options represent a radical departure from the current system and are viewed as politically unrealistic, at least in the short term.

TABLE 2. *Fee Variations in 3 IPAs, 1986 Fees ($)**

Operation	Plan #1	Plan #2	Plan #3
Appendectomy	645	950	1111
Cholecystectomy	1055	1465	1710
Cataract removal	1280	1650	1980
Hip replacement	2808	3666	4274
CABG (3-vessel)	4690	6123	7139

* Plan names withheld because fees were given in confidence to Health Policy Institute by IPA executives.

Several interim remedies are being devised, however. One approach adjusts a few fees that are grossly out of line. Invoking "inherent reasonableness" authority, HCFA uses this approach to reduce payments for "overpriced" procedures. Although corrections have been made for a few services such as cataract removal and installation of pacemakers, most physician payments currently are based on historic trends.

Another approach used by HCFA to control "runaway" costs involves a recalculation of the Medicare Economic Index (MEI), an inflation index for increases in physician office expenses that result from inflation.[7] HCFA estimates that this downward modification in the MEI will save Medicare an increasing amount of money.

Another approach, more far-reaching in concept than the interim measures described previously, but less radical than capitation and physician DRGs, was tried by the Boston University Health Policy Institute (BUHPI) in the fall of 1984.[8] BUHPI compiled a group of 12 Massachusetts surgeons in a pilot effort to develop a complexity-severity index (C/S index) of surgical services, based on professional judgment, that could provide the basis for a relative value scale.

Building this kind of index, although intuitively appealing, proved time consuming and cumbersome. It also raised questions of antitrust. The Federal Trade Commission has barred professional groups from developing relative values guides on the grounds that such guides ". . . established by competitors in a commercial context, probably would constitute illegal price fixing because the dissemination of information and agreement on establishment of price structures usually lead to price uniformity and stabilization."[9]

In this pilot study, BUHPI identified a private corporation that had captured the essence of the C/S index and developed a practical way to convert it to a physician payment management system. The approach of Caterpillar Corporation (CAT), based in Peoria, Illinois, has resulted in the evolution of "degree of difficulty" relative value scales (DODRVS) and regional multipliers that appear to accomplish a pragmatic fee schedule reform. Access to physicians is achieved for CAT employees and their families, and local physician acceptance of the overall CAT process is maximized. Since CAT is not a dominant payer in any geographic area and is not a provider, the potential for antitrust challenges is minimal.

Table 3 shows the close correlation between the C/S index numbers, arrived at through the BUHPI study, and CAT's DODRVS, reached by consultation with regional surgeons. This striking correlation between the two processes suggested to the BUHPI that CAT was on target in its surgical fee activities, and led to the collaborative project described in this paper.

TABLE 3. *BUHPI C/S Index Compared with CAT DODRVS*

	C/S Index	DODRVS
Thoracentesis	3	3.4
Appendectomy	24	26.4
Cholecystectomy (with common bile duct exploration)	48	47.7
Total thyroid lobectomy	40	41.3
Modified radical mastectomy	45	47.7
Colectomy, partial	55	54.5
Pancreatoduodenectomy	100	100.0

The Caterpillar Method

CAT is an international manufacturer of earthmoving machinery and equipment, employing an estimated 54,000 employees in 15 domestic and 13 foreign plants. CAT health benefits cover employees and dependents, as well as 21,000 retirees. The benefit package includes hospitalization, physicians' services, laboratory, x-ray, prescription drugs, and dental and eye care. The CAT health plan is self-insured and self-administered.

In 1983, CAT implemented for its U.S. employees a negotiated fee schedule approach to physician fees for surgical and invasive procedures. The CAT physician payment system emphasizes (1) employee access to a wide range of qualified surgeons, (2) fees negotiated with local surgeons that are considered reasonable and consistent with local market forces, and (3) billing practices review applied consistently to all incoming claims. Particular features of this approach are described below.

Establish a fair fee cap. With input from respected community physicians in locations with a large number of CAT employees, CAT establishes a fair fee cap for surgical services. The CAT method involves convening a limited number of meetings with selected representatives of the surgical community and the CAT medical director for group insurance (CAT M.D.). Where it makes the most efficient use of time, the CAT M.D. meets with individual specialty groups. Operating under a "physician friendly" philosophy and the assumption that physician education and involvement help achieve a mutually agreeable solution, the CAT M.D. describes the situation from CAT's point of view: (1) there are wide variations in fees and billing practices; (2) there is often insufficient documentation to properly process claims; (3) a way is needed to compare the difficulty of various services so their "relative value" can be considered for payment decisions; and (4) a reassessment of the need for surgical assistants is needed.

Actual claims received are used as examples (with patient and provider identities protected). The CAT M.D. then solicits provider input on how problems can be corrected. General consensus is gained on reasonable billing practices and relative degree of difficulty of various procedures, based on recommendations by the CAT M.D. and discussions with physician groups.

Use of geographic multipliers. CAT's DODRVS is combined with a regional dollar multiplier to calculate the actual dollar payment limit. The regional multiplier is based on market research by the CAT M.D. Where there are unusual market conditions for certain specialties, CAT may adjust the multiplier up or down for some services rather than changing the entire region's multiplier. This system allows CAT to take into account the local health care market, legitimate variations in provider billing and medical practices, and variations in the cost of living.

Continual audit and recoding of physician bills. CAT claims processors subject each incoming physician bill to a coding analysis of CPT-4 codes as a first step, and recode claims where irregularities are found. Obvious simple coding errors are corrected first. Individuals with clinical knowledge and judgment then compare the provider's description of services with submitted codes; operative reports are requested for most surgical claims and follow-up calls to provider offices for clarifying information are common. Once the claim reviewer is satisfied that enough information is available to code the bill consistent with CAT procedures, recoding is finalized, and the correct codes are compared with established regional fee schedules. Reviewers with clinical experience consult the CAT M.D. as needed, assuring that a high level of understanding of the surgical experience is applied in the review process.

Tables 4–7 illustrate some features of the CAT process. They are representative of some claims received by CAT.

In Table 4, the appropriate payment is $1000 for code 38100. The patient was hospitalized for an elective splenectomy. The CAT reviewer would disallow codes and

TABLE 4. *Bundling of "Unbundled" Bill*

Procedure	CPT Code	Charge
Splenectomy	38100	$1000
Laparotomy	49000	600
Appendectomy	44950	600
Preoperative check (in hospital)	90215	125
Suture removal	90270	100
Total charge		$2425
Amount paid		$1000

TABLE 5. *Excessive Fee Reduced, Assistant Surgeon Claim Denied as Not Medically Necessary*

Procedure	CPT Code	Charge
Excision biopsy, breast (R)	19120	$1500
Excision biopsy, breast (L)	19120-50	1500
Charge		$3000
Assistant surgeon fee (R)	19120-80	$1200
Assistant surgeon fee (L)	19120-50-80	1200
Charge		$2400
Total charge		$5400
Amount paid		$ 750

charges for all except the splenectomy: a charge for laparotomy and incidental appendectomy is warranted only if done as a separate procedure and preoperative check and postoperative care are conventionally part of the global surgery fee. A charge of $1000 for the splenectomy is in line with the regional fee schedule and is the amount ultimately approved.

In Table 5, the appropriate payment is $750 to the primary surgeon for code 19121 (excision biopsy, breast, bilateral). Under most conditions, one surgeon can perform a breat biopsy. The operative report indicates no unusual circumstances. The assistant surgeon is not reimbursed, and the patient is informed of CAT's review decision.

In Table 6, the appropriate regional payment is $60 for code 17100. The procedure was actually a simple wart removal. The operative report describes a 0.25-inch plantar wart on one foot. Excision combined with use of the laser constitutes excessive treatment for this common condition. Wart removal is most accurately coded as 17100 ("destruction by any method of benign skin lesion").

CAT knows that four local experienced, board-certified cardiac surgeons will carry out a three-vessel coronary artery bypass for $5000, assuring that access can be achieved for that fee (Table 7).

Tables 4–7 demonstrate that complete and knowledgeable recoding of claims requires familiarity with both the content of various surgical procedures and the details of coding surgical services.

Physician negotiations. Individual physician negotiations are carried out for selected claims. After establishing an overall fee schedule with local physician representatives, CAT continues its negotiations on a selected claim-by-claim basis. If the amount charged for corrected codes significantly exceeds the regional fee cap, CAT contacts the billing physician, giving information on the corrected codes and the amount allowed. The CAT M.D. makes many of these calls. Usually the provider is willing to accept CAT's recoding and reduced fee. Discussions of claims with physicians have revealed that providers enter practice largely ignorant of common billing practices. Most admit they do not know what various procedures are worth. At best they occasionally may ask other providers what they charge. Those who use an RVS have access only to a wide variety of unstandardized sources. Some are advised to start charging high rates to get a high fee profile. Often, physician offices have an office clerk coding claims who is not trained in medical terms or coding, whereas other physicians rely on central billing services that promise to "maximize reimbursement," often with "creative" upcoding or unbundling of services.

TABLE 6. *Recoding of Unnecessary Procedure, Excessive Fee Reduced*

Provider Description	CPT Code	Charge
Excision, benign lesion, foot and use of CO_2 laser	11421	$450
Total charge		$450
Amount paid		$ 60

TABLE 7. *Fee Adjustment*

Procedure	CPT Code	Charge
Coronary artery bypass graft, 3 vessel	33512	$8000
Total charge		$8000
Amount paid		$5000

Employee communication. CAT has a program of employee communication that defines the employees' responsibilities and options when payment is less than the fee charged by a surgeon. A letter of explanation is automatically generated to the employee when there has been a payment reduction. It states that if the employee has discussed the fee with the physician before the procedure, the employee is responsible for the amount in excess of CAT's fee cap. Also, employees are told when their provider has agreed to accept CAT's reimbursement as payment in full.

Patient held harmless. If a physician bills an employee for the amount that exceeds the fee cap, the employee is instructed to contact CAT, and a CAT provider relations specialist discusses the situation with the physician. Patients are not required to pay the physicians' balance bill above the CAT payment (that is, they are "held harmless") if the physicians have not informed the patients of the higher-than-cap fee before the procedure. CAT intervenes on the patient's behalf when the physician refuses to lower his/her fee to the established cap. On average, of about 20,000 physician claims received per year, CAT has less than a dozen instances in which providers insist on trying to obtain reimbursement above the CAT fee through claims court. In over 95% of these cases, the judge has agreed that CAT's payment is reasonable for the services, based on local surgeon input.

Study of Savings with CAT Method

CAT's internal calculations indicate that it achieves significant savings with its surgeon bill review process by reducing fees that otherwise would have been paid in full. The BUHPI is conducting an external evaluation of the CAT process for managing surgeon fees. Standard surgical fee processing by large insurance companies and third-party administrators is being compared with the potential cost savings of the CAT process. The BUHPI has obtained samples of consecutively filed claims for surgical services that have been processed for several large self-insured corporations that administer their claims through major insurance carriers. The benefit plans establish payment caps at a percentile of usual and customary fees, and the carriers' auditing of codes was representative of current industry standards. CAT's recoding and bundling procedures, as well as payment caps, were applied to these claims, with the goal of finding if the savings from payment reduction significantly exceeded those achieved by these carriers.

Hard copies of the providers' originally submitted claims were processed by CAT staff without information about changes from charges that had been made by the carriers before these claims had been paid. Confounding variables of payment due to copayments, deductibles, or coordination of benefits were eliminated.

The total charges included in the sample claims were over $140,000. The carriers adjusted 13 to 15% of their claims and paid 4.3 to 35% less than total charges. CAT adjusted 35 to 40% of these same claims and reduced payment from charges by 22 to 43%. Therefore, CAT would have achieved an additional savings of 8 to 17.7% if CAT's procedures and the lower of CAT or the administrator's fee schedule were used. One third of the additional savings came from coding changes in the original bills and two thirds by the application of the CAT negotiated fee schedule. In some instances providers submitted an incorrect code that significantly *undervalued* the procedure that was done. If the provider's code had been used, the payment would have been cut to an unreasonable level. In these instances, the CAT reviewer "upcoded" to the correct code and allowed the more appropriate fee; the savings potential includes these corrections in favor of billing surgeons.

Discussion

The CAT system for managing surgeons' fees has been developed by a progressive benefit department in a large American corporation. The system depends on detailed knowledge of surgical practice so that recoding and bundling of procedures categorized by CPT-4 codes can be accurately carried out. It requires contact with local surgeons in regions with a high concentration of employees so that market forces can be taken into account in determining an appropriate level of local fees.

An access-oriented negotiated fee schedule can have many permutations. In areas with a surgeon surplus, a corporation may be able to negotiate lower fees with surgeons than those previously paid. In areas with few surgeons, fees lower than customary are more likely to create patient access problems should the surgeons resist reductions negotiated elsewhere. Still, modified versions of CAT's approach would be similar to processes already used by the government in establishing "inherent reasonableness" for cataract extraction and pacemaker installation fees.

The key concern about any new surgeon payment approach should be the ability to attract a good representation of local surgeons who will accept it. Ensuring employees' access to qualified surgeons is the paramount goal. All other considerations, even inherent reasonableness of lower fees because of technological advantages or cost containment, should remain secondary.

Based on the BUHPI's analysis, the CAT process is a workable and market-tested solution to the need to balance access and cost management. It is suitable for large corporations such as CAT with both self-funded and self-administered health benefits. It can also be used (after eligibility is certified and benefits are coordinated) by claims processing systems. Accurate implementation of the CAT process requires (1) hard copies of the CPT-4 codes submitted by the surgeon and availability of the operative notes, to reconcile discrepancies between CPT-4 codes and the surgical service, and (2) access-oriented negotiated fee schedules obtained by applying a geographic multiplier to an RVS, such as CAT's DODRVS.

State and federal governments can modify the CAT process for Medicaid and Medicare, with the same goals that motivate the private sector: access and cost management. Regional fee schedules could be established with national DODRVS values and regional multipliers based on market forces. Balance billing is optional, using the CAT model. However, its effectiveness as a cost management approach is strengthened with its "hold harmless" provision. In the CAT system, if a patient knows a surgeon is charging a fee higher than the negotiated fee, the patient is responsible for the balance. If no discussion has occurred, the patient is held harmless for bills in excess of the fee cap.

If adequate access is to be preserved without the need for balance billing, payments must be established so that a majority of qualified surgeons in each region will accept the negotiated fee as payment in full. If this acceptance is not achieved, then access problems will arise, as

TABLE 8. *Comparison of "Resource-based Relative Value Scale" (RBRVS) and "Access-oriented Negotiated Fee Schedule" (AONFS) for Physician Reimbursement**

	RBRVS (Hsiao)	AONFS (CAT)
Goal	A "comparable worth" reform for physicians, a group with high incomes relative to most other occupations.	Patient access to local physicians at a negotiated price.
Methodology	Complex formula determines RBRVS; time is a major determinant.	Revision of fees is based on negotiations, M.D. fee acceptance patterns (market forces, not payment of charges).
Application	Two basic problems: (1) RBRVS is not a fee, and knowledge is needed of regional situations to use multiplier effectively, (2) when applied in Massachusetts, shown to need extensive modification to get support of, and access to, local surgeons.	In routine use. CAT knows that well-qualified local physicians will accept the AONFS.

* AONF = DODRVS × regional multiplier.

occurred in 1986 for the Massachusetts Medicaid program. That program was forced to increase significantly its fees for normal deliveries. As stated in the *Boston Globe*, ". . . responding to a crisis in access to obstetrical care in many areas of the state, the panel hiked the all-inclusive fee for pregnancy care and childbirth from $508 to as much as $1,200."[10] This is a good example of the futility of a fee schedule that does not build on knowledge of physicians' availability at different fee levels in each region. The Massachusetts Medicaid program had a previous experience with attempting to introduce a fee schedule based on a "resource-based" formula.

In July 1983, the *Boston Globe* described a new strategy that was suggested by the Massachusetts Rate Setting Commission for the Medicaid program and workers compensation.[11] Based on the 1979 study by Drs. Hsiao and Stason from the Harvard School of Public Health,[12] the Rate Setting Commission proposed that the fees for 21 common surgical procedures should be cut by amounts ranging from 4% to 59%. At the same time, physicians seeing patients in their office were to get 71% more for initial visits. These proposed changes were the estimated relative resource requirements of different physician services, with a strong focus on the time involved. The formulas were established in the Hsiao/Stason analysis of physician practices.

These changes were adopted in September 1983, but on August 23, 1984, the Rate Setting Commission raised the fees that the state Medicaid program paid to doctors for surgical procedures. As stated in the *Boston Globe*, "no prior hearing was held or public notice given before the August reversal because the Commission subsequently said physician resignations from Medicaid had reached the level of a public health emergency. Most striking of these defections were obstetricians/gynecologists."[13] This experience suggests that fees ultimately paid by Medicaid were primarily driven by the need to get access to Medicaid patients to physicians, and not by a formula for "resource costs."

The American Society of Internal Medicine and the American Medical Association have supported an elaborate study of the Hsiao methodology commissioned by HCFA, and there is much speculation about the possible use of an RBRVS for the determination of Medicare fees when it becomes available in the summer of 1988. The investigators of the BUHPI originally believed that the consensus process to determine a C/S index could be developed as the basis for fee reform that would be acceptable and perceived as fair by physicians. However, the consensus approach is laborious, and much time would have been necessary to interrelate all specialties and resolve potential conflicts. It was then that the BUHPI began to study the CAT system, and found that it involved a process with appropriate goals, methodology, and application for cost management and market acceptance.

Table 8 outlines the basic differences between a "resource based" RVS and an access-oriented negotiated fee schedule, as used by CAT. A basic goal of the RBRVS is to "reform" physician reimbursement in the direction of more equity between procedure-oriented specialists and generalists. However, as the evidence suggests, this goal will be in conflict with realities of the marketplace and will result in paying fees that are either unnecessarily high or too low to get ready access for insurees to local physicians.

The methodology of the RBRVS is based on a formula unrelated to local market forces, whereas the access-oriented negotiated fee schedule used by CAT builds on negotiations and local fee acceptance patterns to gain access. The CAT system's ability to adjust for regional differences in the market is the essential difference in the two approaches. The CAT system is in routine use and will continue to be modified by changes in local physician manpower and other factors such as increases in malpractice premiums. We suggest that an access-oriented negotiated fee schedule such as the CAT system deserves consideration as the preferred method of fee reform.

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DISCUSSION

DR. W. GERALD AUSTEN (Boston, Massachusetts): I congratulate Drs. Egdahl and Hertenstein on an excellent and stimulating paper. They have worked long and hard on physician payment reform, and they recognized early the importance of physician acceptance in any proposed reform. Thus, a major element of the current proposal includes the active participation of the physicians.

Three and a half years ago, the Regents of the American College of Surgeons created a Committee on Physician Reimbursement of which I have been Chairman. This committee, with much input from the surgical specialty societies, has developed recommendations for the reform of the Medicare physician payment program, and these recommendations were approved by the Regents in October 1986.

The aim of the College, like the approach presented today, is to identify ways to achieve a more rational payment system with cost savings and at the same time ensuring adequate access to quality care.

The ACS approach has a number of similarities to the program presented this morning; the ACS proposal includes the creation of a Medicare relative value scale based on physician charge data and with modifiers based on geographic differences in practice costs, the definition of payment units with emphasis on a global fee and the creation of definitions and guidelines to determine when an assistant at surgery for Medicare payment purposes is necessary.

I have one question for the authors. The Caterpillar Corporation has approximately 50,000 employees in 15 domestic plants, and it also has a very persuasive, sensible medical director. How would you expand your proposal from one company to a national program?

Finally, I would like to add that it is crucial that surgery be involved as much as possible in the current debate on physician reimbursement reform, and we need to be able to present sensible and fair approaches backed by solid data. The next year and a half is probably going to be crucial.

I would urge Drs. Egdahl and Hertenstein to continue to gather information and to make every effort to present their data and recommendations to the appropriate congressional committees and to the Administration.

DR. OLIVER H. BEAHRS (Rochester, Minnesota): Drs. Egdahl and Hertenstein have done us a favor by developing and reporting a modification of the CPR fee for service reimbursement for surgical services. I appreciate the opportunity to have read the manuscript.

Their program, which is a negotiated access RVS, is in contrast to the Harvard–AMA resource based RVS, and is being developed under contract from HCFA. This RVS is of concern because of the inordinate weight given to time as a factor and the methodology being used.

There is great anticipation regarding this study in Washington and some are thinking of it as the only game in town.

The Physician Payment Review Commission (PhysPRC) established by Congress in 1986 made its first report to Congress on March 1, 1987. The Commission supports a fee scale based on a national RVS with appropriate regional multipliers to determine fees. The basis for the RVS has not been determined, but hopefully it might be based somewhat on historic charges and not the strictly resourced criteria of the based parameters used in the Harvard Study.

The use of the CPT-4 Code has come under criticism: first a dictionary of 2000 codes, and now 7000 and with multipliers 48,000. It was established primarily for medical record keeping not to establish charges. It has led to unbundling of services and upcoding to establish fee for services. This practice has led to excessively high fees in at least 10% of cases because of unbundling or upcoding.

I would be interested in the author's suggestions how the CPT-4 codes might be collapsed or bundled and what policy could be established to prevent these abuses.

A long-term program for physician payment is probably several years away and may be a fee scale hopefully, but there is administrative and congressional support for capitation or voucher arrangement, possibly DRGs. Congress is looking for a near-term solution to its budget problem for 1988.

The budget mark-up will be in the next few weeks and the recommendations to meet the cut almost certain in physician reimbursement will be in place by September.

The reduction in reimbursement might be another freeze, a shaving downward of the medical economic index, selecting the high-cost outliers such as coronary artery bypass, hip reconstruction, and/or TUR for across-the-board decreases as was done to cataract surgery in 1986 and 1987, or selective decrease in the high rollers or by addressing the reduction by using the inherent reasonable rule that is already in legislation.

My second question to Dr. Egdahl and Dr. Hertenstein is: what are your recommendations in the next month or two to meet the 1988 budget limits?

DR. MARTIN ALLGÖWER (Basel, Switzerland): I appreciate the invitation to look "with a Swiss eye" at the presentation of Dr. Egdahl.

In Switzerland it is said that the surgeon goes through two stages: At the beginning of his career, collecting a fee, he gets red in the face. Later on his face reddens when he does not get paid!

The Swiss economic system is a rather complex mixture of free enterprise and institutions run almost exclusively by public bodies. We consider many of the things you do not as public responsibilities. These include post and telephone services, railway services, schooling and university formation, and most hospitals are run by local government agencies. The health care system is furthermore complicated by the fact that insurance conditions for accidents are very different from those for diseases. It is obvious that this difficult distinction keeps our lawyers busy!

Basically, surgeons are mostly employed on a geographical full-time basis in a state hospital. Those state hospitals, however, have private, semiprivate, and general wards. This, I believe, is a rather favorable arrangement, combining a salaried position for the administrative obligations as well as for the care of the general patient with a fee-for-service system for the private patients. Now, comparing this with the cap system, we find great similarities because the Union of Swiss Surgical Societies, including all specialties, has set up a range of fees that may be reasonably asked from a patient or from the insurance, *i.e.,* the third party paying. Those ranges, just to give you an idea, would range from 400 to 1000 francs for an appendectomy, for a gallbladder from 1000 to 2000 francs, and for major operations such as a total gastrectomy, a Whipple, an acetabular repair or a resection of an abdominal aneurysm, from 3000 to 6000 Swiss francs. That is about the maximum fee we are allowed to ask or, at least, that the Union will support, if it is contested in court. You may divide the figures by 2 to arrive at dollar values, because that is about the realistic comparison in terms of buying power.

It is a fairly democratic self-regulating peer controlled system. What we dislike in Switzerland is the "big brother" state watching us and telling us what to do.

We have one advantage over you. The contingency system is unacceptable and the one party who loses "the battle" usually has to pay the other's legal expenses. That often prevents people from going to court, although there has been a definite increase in liability claims in recent years.

Overall our system results in an average income of some 300,000 to 400,000 francs for a Swiss surgeon. Out of that he pays some 50% in taxes. Our rather democratic system is similar to what Dr. Egdahl has just presented. It is based on a fee for service "common sense scale," the majority of surgeons working in a geographical full-time scheme.

DR. WILLIAM R. DRUCKER (Rochester, New York): I appreciate the opportunity I had to review this paper. Dr. Egdahl has given us a clear presentation of an industry-sponsored plan that attempts to gain physician compliance with a method of reducing costs of medical care through reduction in fees.

It is a very clear example that in addition to government today, our health care system is being strongly influenced by industry.

I have a couple of editorial comments and then a couple of questions. The major factor in the rise in health care costs is not physician fees. This is simply illustrated by a look at the average fees of physicians across the country, somewhere in the range of $50,000–$150,000. I realize that others make considerably more, but each physician can be estimated to cost the health care system something in the order of three quarters of a million dollars per year by the exercise of his physician rights in doing his job of taking care of patients. Therefore, the major target that needs to be addressed is physician behavior, not physician fees. Nevertheless, fees are perceived as a problem that is going to be addressed whether we like it or not.

I wonder whether this paper is simply the expression of a last gasp hope that current physician fees and the fee for service system will continue. I sincerely hope this is not its purpose and I believe Dr. Egdahl agrees based on the way he has presented the paper. My reading from the paper is that Dr. Egdahl is presenting a plan that is asking clearly for physicians to get together and plan to help solve the problem of fees rather than having it done for us by external agencies; that means industry and government.

My questions are these. They are straightforward, I believe, and can be answered simply. What will happen in the case of an emergency when one of the patients in the system under the cap must have an emergency operation and they seek a doctor who does not agree with the system: would this be settled in claims court?

What about quality? Does the system depend on the physician participants to ensure quality or do they have other ways to ensure that their employees are obtaining the quality of care that they would under the current system of fee selection.

How about comparison with other systems? Has there been enough experience to date to show that this system is gaining popularity? Is there any way to compare this system with others in terms of two factors: physician acceptance to work in the system, and employee acceptance of this system for their health insurance?

Then there is a question of cost. This is a very complex system. It seems very costly if one reads carefully. What is the cost? Is there any estimate of what the cost would be of setting up and maintaining this system that requires close scrutiny of all bills that come in; a very complex system of monitoring these bills? Is the billing method unique to CAT or can other insurance systems do this too? Is this system for sale? Do other insurance companies look at claims this carefully?

DR. BENSON B. ROE (San Francisco, California): Dr. Egdahl is to be thanked for bringing to our attention a sensible proposal to address a serious threat to the fee-for-service system. I believe we finally are all aware of this threat, and I am delighted that we are prepared to gather our forces to get behind something positive.

About 8 years ago I became aware of the enormity of the abuses to the current system that were taking place, perhaps not by the respectable members of our profession but by an alarming number of those who did the kind of unbundling and some of the things that he showed you. I published an article that was intended to stir us to take some initiative in this problem rather than hoping it would go away. I hope it is not too late.

It is equally important that we get behind some system that establishes fiscal integrity so that we do not jeopardize the precious and unique privilege that we have of self-governance. This privilege is threatened by the behavior of some of our colleagues who have abused the system and brought this problem to our attention.

In addition to the proposals that Dr. Egdahl has made, I believe we should place emphasis on the magnitude of responsibility to cover not only accessory procedures but complications. No one can tell me whether my complication was part of the patient's underlying disease or could possibly be one from some flaw in my technique or management. We should accept as a part of our primary responsibility the full scope of managing a patient from start to finish without throwing in extra for everything that can be imagined. If we had done that, we would have reduced our total cost to the public by at least 20%.

DR. JAMES R. JUDE (Miami, Florida): I rise because I am confronted by patients who are faced with billing problems after hospital discharge. One of the problems is the unbundling that Dr. Egdahl has brought up.

Ten years ago on an Ethics Committee of our local medical society we, out of hand, tossed unbundling out as a completely immoral approach to any type of billing. I did not believe it even could possibly exist any more, but there is more of a problem than just the bundling together of the surgical fee. The problem is much greater than that. We always keep our office open to speak to any patients about any problems, and it is very common for them to present with bills of what really amounts to an unbundling of the bills of other physicians who were involved in their treatment.

Most commonly this has applied to anesthesiology, which frequently approaches 50% of the surgical fee. It is not, however, only the anesthesiologists, it is also the internists, the radiologists, the pathologists, and possibly the cardiologists who are reading electrocardiograms. Patients receive an enormous number of bills from physicians, and so it is a total physician unbundling and not just a surgical fee unbundling that is occurring.

Some way or other we have to approach the problem whereby there will be some type of bundling together of all physician fees as a package.

As our President presented yesterday in his Presidential Address, many treatments that we do are not all surgical anymore, but rather a blending over into medicine, and medicine is delivering surgery and surgery is delivering medicine. Therefore, we should give a great consideration to the total care and the total charge.

Dr. Egdahl, what if anything have you considered about these other fees in respect to a global cap or other industry approaches to the total cost of care in surgery?

DR. JONATHAN E. RHOADS (Philadelphia, Pennsylvania): I listened to this paper with a great deal of interest. I would emphasize that if most people have a 50% overhead, that a 15% reduction in fee is a 30% reduction in take-home remuneration. That is well to keep in mind.

There is one aspect of the overhead that has gotten bigger and that is liability insurance. This in a way is the loose cannon on the deck, and when you have a fee schedule set, whether by government or by consent, and this expense is assumed to be something that the physician will pay, you have an unpredictable situation.

I raise the question and ask the authors if there is any precedent for malpractice insurance being billed on a per case basis or a percentage of the fee. No doubt this would require the insurance company to have access to one's tax returns and so forth to be sure that it was honest, but it would have certain great advantages. It would permit the young physician starting out to start out on his own, pay his share of the liability costs, but not be expected to pay immediately the same amount that a person would be paying who is doing 10 times as much work in the middle of his career.

Perhaps the far greater advantage in my belief is that this could appear and should appear as a separate item on the bill.

I can think of no way that would educate more of the public as to the true cost of liability insurance than to have a bill (operation $300, insurance $125, or whatever it might come to).

I rose to raise this issue and to ask the authors if they knew if there was any precedent for such a plan and to ask whether they believe there is any way this could be tried out before we get tied into a fee schedule system with an unpredictable cost for liability insurance.

DR. RICHARD H. EGDAHL (Closing discussion): Dr. Austen's question about the possibility of expanding the Caterpillar program as it now exists to a national level is an important one. The problem is that major national programs such as Medicare necessarily involve a large bureaucracy, whereas a private self-administered company such as Caterpillar does not require the same degree of routinization of operations and an easily replicated methodology. The country could certainly be divided into 6–12 regions, each consisting of several states. I do not know whether appropriate flexibility could be built into the management and technical components of the administrative structure which would be part of a national program.

Dr. Beahrs raises questions about the future use of CPT-4 codes and asks what we can do in the short range to control outlier Medicare fees. I believe we can use CPT-4 as long as we understand the basis for matching up the procedures that actually were carried out with the codes, and have some way to ratchet downward those charges that seem inappropriate. Certainly there are a few groups selling systems with the goal of achieving code creep, which is basically dishonest. On the other hand, the majority of codes that are incorrect represent simple errors based on the difficulty of each doctor's office knowing all the technicalities of coding. We can stick with CPT-4, but must match the operative note with the CPT-4 code, using physician judgment to determine if the code is appropriate. The short-term answer for HCFA is to expand the principle of inherent reasonableness, which thus far has been limited to a few surgical conditions. Another 20–30 big-ticket items that appear to be out of line could be revised downward or upward.

Dr. Martin Allgöwer from Basel talked about the Swiss system and the apparent success of physician-sickness fund negotiations. This type of negotiation, with the government playing a catalytic role, might have relevance to the U.S. system in the private sector. However, Medicare will probably demand a closer involvement in the process than exists in Switzerland, since the government is paying the bill directly.

Dr. Drucker asked a key question about what happens in emergencies under the Caterpillar system. Usually Caterpillar pays charges in emergencies, but also has a strategy involving clearance for appropriateness of treatment in emergencies, when there is time. If gross overcharges are billed, even for emergency situations, and local surgeons support that the charges are unreasonable, then payment of those charges can be challenged.

Dr. Roe discussed his analysis of fees, and raised the question about possible antitrust issues if physicians are in the position of commenting on the appropriateness of their fees. Industry does not want to see private medicine nationalized, but could turn on us if we do not cooperate in developing a rational method of physician reimbursement. The key to not raising antitrust issues is for surgeons to act as individual consultants to payers who determine those fees, such as large industry.

Dr. Jude asked about how to get our internist colleagues involved in the process of fee negotiations. We found in our complexity/severity work with the Massachusetts Chapter of the American College of Surgeons that we could relatively easily get consensus on the "relative value" or "complexity/severity" of surgical services among that group. We then talked to internists and achieved some preliminary agreements; for example, an "intermediate acute myocardial infarction," from the time a patient comes into the emergency room, is taken into the critical care unit, and discharged, appeared to be similar in complexity/severity to an uncomplicated cholecystectomy, from initial diagnosis through discharge from the hospital after surgery. Reimbursement for some general medical conditions can be converted into a global fee, but for many medical conditions it is a more difficult process than for surgical cases.

Finally, Dr. Rhoads talked about malpractice problems associated with surgery. I return to the principal goal of Caterpillar and its fee process, which is access for their employees and their families to a significant number of high-quality local surgeons. Overall, malpractice problems will probably get worse before they get better. A solution will flow from severe access problems in different parts of the country, and a realization by both legislators and the public that the ordinary rigors of surgical practice are being compounded manyfold by additional financial and psychological pressures from the omnipresent danger of malpractice suits. We suggest that the Caterpillar process of negotiating access-oriented maximal fees with local surgical groups represents a reasonable compromise between paying charges, on the one hand, and accepting a formulaic-driven fee schedule not negotiated with some local physicians with access as a goal, on the other hand.

Increases in malpractice premiums will result in increased surgical fees, or the public will not have available the surgeons that they want in the variety of practice sites and numbers of specialties that are desired. We have only a modest amount of time before HCFA and the Congress will take some kind of action on fees, as they have on hospital reimbursement under Medicare. Industry can be our strongest ally in achieving a workable system of access-oriented negotiated fees.

Improved Hospital Morbidity, Mortality, and Survival after the Whipple Procedure

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Between 1969 and 1986, 88 patients had a Whipple resection for adenocarcinoma of the pancreas (N = 50), ampulla (N = 19), distal bile duct (N = 10), and duodenum (N = 9). Forty-nine patients were men, 39 were women, and the mean age was 58 years (range: 34–84 years). The patients were divided into two groups on the basis of two different time periods: those operated on from 1969 to 1980 (N = 41) and those operated on from 1981 to 1986 (N = 47). There were no significant differences between the two groups in terms of mean age, sex distribution, duration of symptoms before presentation, or mean weight loss. Likewise, preoperative laboratory data were similar for both groups of patients. In addition, mean tumor size for patients with pancreatic cancer (3.5 cm *vs.* 3.2 cm) and patients with nonpancreatic periampullary cancer (1.9 cm *vs.* 2.2 cm) was similar in both groups, as was the incidence of positive lymph nodes. Among the 41 patients operated on during the first period, hospital morbidity and mortality rates were 59% and 24%, respectively. In contrast, hospital morbidity and mortality rates were 36% and 2%, respectively, among the 47 patients operated on during the recent period. During the recent period, more Whipple procedures were performed each year (7.8 *vs.* 3.4) and by fewer surgeons (3.4 operations/surgeon *vs.* 1.9 operations/surgeon). In addition, between 1981 and 1986, there were fewer total pancreatectomies (9% *vs.* 39%), fewer vagotomies (26% *vs.* 76%), and more pyloric-preserving procedures (30% *vs.* 0) performed compared with the earlier period. During the recent period, mean operative time (7.8 *vs.* 9.0 hours), mean estimated blood loss (1694 *vs.* 3271 mL), and mean intraoperative blood replacement (3.6 *vs.* 6.3 units) were all significantly less than in the earlier period. These findings suggest that the recent decline in operative morbidity and mortality may be due to fewer surgeons performing more Whipple resections in less time and with less blood loss. The actuarial 5-year survival rate for the 38 patients with nonpancreatic periampullary cancer was 34%. Surprisingly, the actuarial 5-year survival rate among the 50 patients with pancreatic cancer was 18%. Moreover, in the absence of positive lymph node involvement, the 5-year actuarial survival rate among patients with pancreatic cancer was 48%. No explanation is obvious for the improvement in survival among patients with pancreatic cancer.

THE FIRST SUCCESSFUL RESECTION of a periampullary carcinoma in the United States was performed by Halsted in 1898.[1] The tumor was merely excised locally, and the patient died 7 months later of tumor recurrence. Whipple and colleagues,[2] in 1935, described the first pancreaticoduodenectomy performed for a periampullary carcinoma. The procedure was performed in two stages. The operation subsequently underwent modifications, and was first reported as a one-stage procedure by Trimble and Associates[3] in 1941. Thereafter, the pancreaticoduodenectomy became the operation of choice for patients with cancer of the head of the pancreas, ampulla, distal bile duct, and duodenum. However, during the 1960s and 1970s, some suggested that the Whipple procedure should be abandoned for the management of pancreatic cancer because of a high operative mortality rate, and virtually no long-term survivors.[4–6] Recently, several reports have suggested a sharp decrease in morbidity and mortality for the Whipple procedure,[7–9] as well as significantly improved survival for all periampullary tumors, including adenocarcinoma of the pancreas.[9,10] We have reviewed the experience with the Whipple procedure over an 18-year period at the Johns Hopkins Hospital to determine whether similar trends were evident in our patients.

Clinical Material

Between January 1969 and May 1986, 108 patients had an elective Whipple resection at the Johns Hopkins Hospital. Periampullary carcinoma was the indication

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TABLE 1. *Patients Undergoing Pancreaticoduodenectomy for Periampullary Carcinoma**

	1969–1986 (N = 88)	1969–1980 (N = 41)	1981–1986 (N = 47)	p
Operative indication				
Pancreatic cancer	50 (57)	26 (63)	24 (51)	NS
Ampullary cancer	19 (22)	7 (17)	12 (26)	NS
Bile duct cancer	10 (11)	4 (10)	6 (13)	NS
Duodenal cancer	9 (10)	4 (10)	5 (11)	NS
Mean age	58.4 ± 1.1	59.1 ± 1.5	57.8 ± 1.6	NS
Sex				
Male	49 (56)	24 (59)	25 (53)	NS
Female	39 (44)	17 (41)	22 (47)	NS
Race				
Black	20 (23)	11 (27)	9 (19)	NS
White	68 (77)	30 (73)	38 (81)	NS
Symptoms				
Jaundice	72 (82)	35 (85)	37 (79)	NS
Weight loss	66 (75)	32 (78)	34 (72)	NS
Mean weight loss (lbs)	14.4 ± 1.6	16.1 ± 2.1	12.1 ± 2.0	NS†
Abdominal pain	46 (52)	20 (49)	26 (55)	NS
Mean duration of symptoms (weeks)	8.1 ± 1.2	8.2 ± 1.5	7.8 ± 1.9	NS
Physical findings				
Hepatomegaly	28 (32)	18 (44)	10 (21)	<0.05
Palpable gallbladder	20 (23)	11 (27)	9 (19)	NS
Occult fecal blood	24 (27)	9 (22)	15 (32)	NS
Palpable abdominal mass	3 (3)	1 (2)	2 (4)	NS
Medical illnesses				
Diabetes mellitus	15 (17)	8 (20)	7 (15)	NS
Coronary artery disease	8 (9)	4 (10)	4 (9)	NS
Obstructive lung disease	6 (7)	3 (7)	3 (6)	NS
History of smoking	46 (52)	24 (59)	22 (47)	
Previous exploration	15 (17)	7 (17)	8 (17)	NS
Laboratory data				
Hematocrit (%)	37.1 ± 0.54	37.5 ± 0.71	36.8 ± 0.80	NS
WCB (10^6/mm^3)	8.1 ± 0.37	7.7 ± 0.59	8.4 ± 0.46	NS
Total lymphocyte count	1854 ± 163	1786 ± 192	1941 ± 236	NS
Bilirubin (mg/dL)	9.4 ± 0.75	10.1 ± 1.11	9.0 ± 0.97	NS
Alkaline Phosphatase (IU/L)	510 ± 40.8	612 ± 68.7	425 ± 44.3	<0.05†
SGOT	163 ± 13.8	182 ± 22.3	146 ± 16.9	NS†
Albumin (g/dL)	3.7 ± 0.06	3.7 ± 0.10	3.8 ± 0.07	NS
Prothrombin time (secs)	12.4 ± 0.12	12.8 ± 0.21	12.1 ± 0.13	NS
Creatinine (mg/dL)	1.04 ± 0.3	1.05 ± 0.3	1.04 ± 0.4	NS

* Numbers in parentheses represent percentages.

† Wilcoxon nonpaired rank sum test.

for surgery in 88 of the 108 patients. Of these 88 patients, there were 50 with adenocarcinoma of the head of the pancreas, 19 with adenocarcinoma of the ampulla, 10 with adenocarcinoma of the distal bile duct, and nine with adenocarcinoma of the duodenum. The remaining 20 patients had pancreaticoduodenectomy for a variety of other benign and malignant diseases, and were excluded from this review.

Of the 88 patients with periampullary tumors, 49 were men and 39 were women (Table 1). Sixty-eight patients (77%) were white and 20 (23%) were black. The patients ranged in age from 34 to 84 years with a mean age of 58.4 years. Jaundice was the most common presenting symptom and was present in 72 patients (82%). Weight loss occurred in 66 patients (75%). Mean weight loss for these 66 patients was 14.4 ± 1.6 pounds. Abdominal pain was present in 46 patients (52%). The mean duration of symptoms before hospitalization was 8.1 ± 1.2 weeks. Physical findings included hepatomegaly in 28 patients (32%), a palpable gallbladder in 20 patients (23%), and a palpable abdominal mass in three patients (3%). A previous history of adult onset diabetes of at least 2 years' duration was present in 13 patients (15%). Two additional patients (2%) had new onset diabetes mellitus. Eight patients (9%) had a history of significant coronary artery disease and six patients (7%) had chronic obstructive pulmonary disease. Fifteen patients (17%) had had a recent laparotomy before referral to this hospital. Mean laboratory data (Table 1) on admission to the Johns Hopkins Hospital included a hematocrit of 37%, white blood cell count of 8100, total lymphocyte count of 1854, a bilirubin level of 9.4 mg/dL, alkaline phosphatase level of 510 IU/L, SGOT of 163 IU/L, serum albumin level of 3.7 g/dL, prothrombin time of 12.4 seconds, and serum creatinine level of 1.04 mg/dL.

In an effort to detect recent trends in operative mor-

TABLE 2. *Operative Data for Patients Undergoing Pancreaticoduodenectomy**

	1969–1986 (N = 88)	1969–1980 (N = 41)	1981–1986 (N = 47)	p
Operation performed				
Total pancreatectomy	20 (23)	16 (39)	4 (9)	<0.01
Partial pancreatectomy	68 (77)	25 (61)	43 (91)	<0.01
Pyloric-sparing Whipple	14 (16)	0 (0)	14 (30)	<0.01
Partial gastrectomy	74 (84)	41 (100)	33 (70)	<0.01
Concomitant vagotomy	43 (49)	31 (76)	12 (26)	<0.01
No vagotomy	45 (51)	10 (24)	35 (74)	<0.01
Operative data				
Operative time (hours)	8.4 ± 0.24	9.0 ± 0.34	7.8 ± 0.31	<0.05†
Estimated blood loss (mL)	2519 ± 263	3271 ± 440	1694 ± 281	<0.01†
Intraoperative blood transfusion (mL)	4.9 ± 0.39	6.3 ± 0.65	3.6 ± 0.37	<0.01†
Whipple resections per year		3.4	7.8	
Whipple resections per surgeon		1.9	3.6	

* Numbers in parentheses represent percentages.

† Wilcoxon nonpaired rank sum test.

bidity and mortality, the patients were divided into two groups on the basis of two time periods: those operated on between 1969 and 1980, and those operated on between 1981 and 1986. Forty-one patients were operated on during the first period, and 47 patients had a Whipple resection during the recent period.

Comparison of the two groups revealed no significant difference in terms of mean age, sex distribution, race, presenting symptoms, duration of symptoms, physical findings, or associated medical illnesses. Moreover, all preoperative laboratory data were similar in both groups of patients (Table 1).

Operative Management

Among the 88 patients, 68 (77%) had a Whipple operation that included resection of the head, neck, and uncinate process of the pancreas (Table 2). The remaining 20 patients (23%) had a Whipple operation that included a total pancreatectomy. Of the 20 patients managed by total pancreatectomy, 16 had carcinoma of the pancreas, two had carcinoma of the distal bile duct, one had carcinoma of the ampulla, and one patient had duodenal carcinoma. A pyloric-preserving Whipple procedure was used in 14 of 88 patients (16%). A truncal vagotomy was performed in 43 of 88 patients (49%).

The management of the pancreatic remnant varied according to the preference of the surgeon. In 55 (81%) of 68 partial pancreatectomies, a pancreaticojejunostomy was constructed by invagination of the pancreatic remnant into the jejunum, usually in an end-to-end fashion. Five additional patients (7%) had a mucosa-to-mucosa anastomosis between the pancreatic duct and jejunum. In eight patients (12%) the pancreatic duct was ligated and the pancreatic remnant oversewn without the formation of a pancreatic-enteric anastomosis.

Over the 18-year period, the mean operative time for all 88 patients was 8.4 ± 0.24 hours, the mean estimated blood loss was 2519 ± 263 mL, and the mean intraoperative transfusion requirement was 4.9 ± 0.40 units (Table 2). Compared with the 20 patients managed by total pancreatectomy, mean operative time was significantly less for the 68 patients treated by a partial pancreatectomy (9.5 ± 0.52 hours *vs.* 8.1 ± 0.25 hours, $p < 0.05$). However, mean intraoperative blood loss (3014 ± 464 mL *vs.* 2286 ± 312 mL, $p = 0.10$) and mean intraoperative transfusion requirement (5.9 ± 0.65 units *vs.* 4.7 ± 0.48 units, $p = 0.11$) were not significantly different between the two groups.

Mean tumor diameter was 3.4 ± 0.15 cm for the 50 patients with adenocarcinoma of the head of the pancreas and 2.1 ± 0.20 cm for the 38 patients with adenocarcinoma of the ampulla, distal bile duct, and duodenum. Pathologic examination of the resected specimen revealed positive regional lymph nodes in 37 of the 50 patients (74%) with adenocarcinoma of the pancreas and 19 of the 38 patients (50%) with adenocarcinoma of the ampulla, distal bile duct, and duodenum (Table 3).

When one compares the two periods, there were a number of differences in the operative management of the two groups of patients (Table 2). Between 1969 and 1980, total pancreatectomy was performed in 16 of 41 patients (39%), whereas only four of 47 patients (9%) had total pancreatectomy during the recent period ($p < 0.01$). A pyloric-preserving Whipple procedure was performed in 14 of 47 patients (30%) operated on between 1981 and 1986, whereas no pyloric-preserving procedures were done during the earlier period. A truncal vagotomy was performed in 31 of 41 patients (76%) operated on between 1969 and 1980, whereas only 12 of 47 patients (26%) had a vagotomy during the recent period ($p < 0.01$).

Between 1981 and 1986, mean operative time (7.8 ± 0.31 hours *vs.* 9.0 ± 0.34 hours, $p < 0.05$), mean estimated blood loss (1694 ± 281 mL *vs.* 3271 ± 440 mL, $p < 0.01$), and mean intraoperative blood replace-

TABLE 3. *Results of Pathologic Examination of Patients Undergoing Pancreaticoduodenectomy**

	Adenocarcinoma of the Pancreas			
	1969–1986 (N = 50)	1969–1980 (N = 26)	1981–1986 (N = 24)	p
Mean tumor diameter (cm)	3.4 ± 0.15	3.5 ± 0.17	3.2 ± 0.27	NS
Positive lymph nodes	37 (74)	19 (73)	18 (75)	NS
Lymph node status				
0 nodes	13 (26)	7 (27)	6 (25)	NS
1–2 nodes	20 (40)	8 (31)	12 (50)	NS
>2 nodes	17 (34)	11 (42)	6 (25)	NS
	Ampullary Distal Bile Duct and Duodenal Carcinoma			
	1969–1986 (N = 38)	1969–1980 (N = 15)	1981–1986 (N = 23)	p
Mean tumor diameter (cm)	2.1 ± 0.20	1.9 ± 0.22	2.2 ± 0.28	NS
Positive lymph nodes	19 (50)	6 (40)	13 (57)	NS
Lymph node status				
0 nodes	19 (50)	9 (60)	10 (43)	NS
1–2 nodes	9 (24)	3 (20)	6 (26)	NS
>2 nodes	10 (26)	3 (20)	7 (30)	NS

* Numbers in parentheses represent percentages.

ment (3.6 ± 0.37 units *vs.* 6.3 ± 0.65 units, $p < 0.01$) were all significantly less than in the earlier period. In addition, during the recent period, there were more Whipple resections performed each year (7.8 *vs.* 3.4) and by a fewer number of surgeons (3.4 operations/surgeon *vs.* 1.9 operations/surgeon). Comparison of the pathologic specimens for the two periods, however, revealed no significant differences between the two groups in terms of tumor size or stage of the disease (Table 3).

Clinical Course

A major postoperative complication developed in 41 of 88 patients for an overall morbidity rate of 47% (Table 4). A major complication occurred in 22 of 50 patients (44%) with adenocarcinoma of the head of the pancreas and in 19 of 38 patients (50%) with adenocarcinoma of the ampulla, distal bile duct, and duodenum. Among the 68 patients in whom a partial pancreatic resection was performed, a significant complication developed in 35 (51%), whereas a major postoperative complication occurred in seven of 20 patients (35%) managed by total pancreatectomy ($p > 0.05$). A significant postoperative complication developed in 36 of 74 patients (49%) in whom a partial gastric resection was performed and in five of 14 patients (36%) who had a pyloric-sparing Whipple procedure.

TABLE 4. *Morbidity and Mortality of Patients Undergoing Pancreaticoduodenectomy**

	1969–1986 (N = 88)	1969–1980 (N = 41)	1981–1986 (N = 47)	p
Overall morbidity	41 (47)	24 (59)	17 (36)	<0.05
Individual complications				
Pancreatic fistula	12 (18)	6 (22)	6 (14)	NS
Sepsis	17 (19)	12 (29)	5 (11)	<0.05
Wound infection	12 (14)	6 (15)	6 (13)	NS
Intra-abdominal abscess	9 (10)	7 (17)	2 (4)	<0.05
Upper gastrointestinal bleeding	9 (10)	6 (15)	3 (6)	NS
Intra-abdominal hemorrhage	6 (7)	5 (12)	1 (2)	NS
Gastric outlet obstruction	25 (28)	10 (24)	15 (32)	NS
Choledochojejunal fistula	6 (7)	3 (7)	3 (6)	NS
Pulmonary embolus	3 (3)	3 (7)	0	NS
Pulmonary edema	6 (7)	4 (10)	2 (4)	NS
Pneumonia	6 (7)	4 (10)	2 (4)	NS
Urinary tract infection	8 (9)	6 (15)	2 (4)	NS
Stroke	2 (2)	2 (5)	0	NS
Renal failure	9	6 (15)	3 (6)	NS
Overall mortality	11 (12.5)	10 (24)	1 (2)	<0.05

* Numbers in parentheses represent percentages.

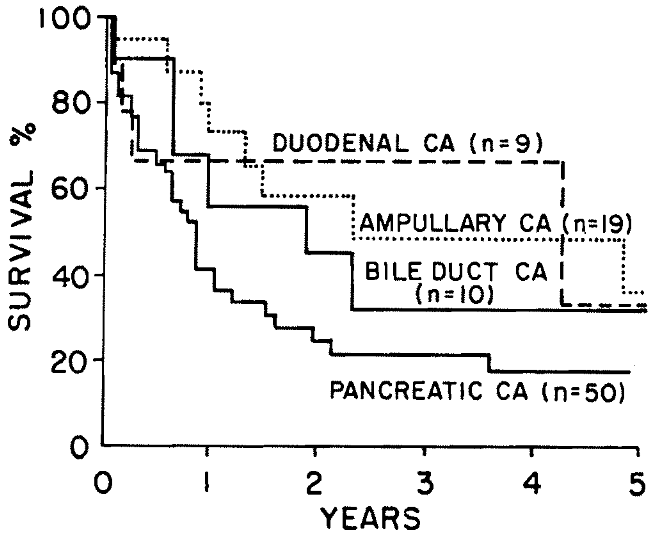

FIG. 1. Actuarial 5-year survival after Whipple resection for patients with adenocarcinoma of the pancreas, ampulla of Vater, distal bile duct, and duodenum.

A pancreatic fistula, defined as the persistent drainage of 50 mL or more of amylase-rich fluid per day for more than 2 weeks, developed in 12 of 68 patients (18%) who had a partial pancreatectomy. Eleven of these 12 fistulas closed spontaneously. One patient required reoperation 2 years after pancreaticoduodenectomy for a persistent fistula. Sepsis occurred in 17 of 88 patients (19%). In eight patients, the septic episode was related to the presence of an intra-abdominal abscess. Septic thrombophlebitis or central line sepsis occurred in five patients, urosepsis occurred in three patients, and cholangitis occurred in one patient. Wound infection occurred in 12 of 88 patients (14%).

An intra-abdominal abscess developed in nine of 88 patients (10%), requiring reoperation or percutaneous drainage. An intra-abdominal abscess occurred in six of 68 patients (9%) in whom a partial pancreatic resection was performed and in three of 20 patients (15%) managed by total pancreatectomy ($p > 0.05$). The presence of an underlying pancreatic fistula did not correlate with the subsequent development of either a wound infection or an intra-abdominal abscess.

Upper gastrointestinal bleeding developed in nine of 88 patients (10%). Bleeding occurred in five of 43 patients (12%) in whom a vagotomy was performed and in four of 45 patients (9%) managed without a vagotomy. One of 14 patients (7%) who had a pyloric-preserving Whipple procedure and eight of 74 patients (11%) in whom a partial gastric resection was performed had upper gastrointestinal bleeding ($p > 0.05$). Postoperative intra-abdominal hemorrhage requiring reoperation occurred in six of 88 patients (7%). Six patients required emergency re-exploration: one on the day of the initial operation, four on the first postoperative day, and one on the second postoperative day.

Temporary gastric outlet obstruction requiring nasogastric decompression for greater than 10 days occurred in 25 of 88 patients (28%). Delayed gastric emptying occurred in 12 of 43 patients (28%) in whom a truncal vagotomy was performed and in 13 of 45 patients (29%) managed without a vagotomy. Four of 14 patients (29%) who had a pyloric-preserving Whipple procedure and 21 of 74 patients (28%) in whom a partial gastric resection was performed had delayed gastric emptying.

In comparing the two periods, a significant decrease in the overall operative morbidity was observed during the more recent time period (Table 4). The overall morbidity rate was 36% among the patients operated on between 1981 and 1986 and 59% for those operated on between 1969 and 1980 ($p < 0.05$). During the recent period, there was a decreased incidence of many individual complications. However, analysis of the individual complications revealed a statistically significant decrease only with the complications of intra-abdominal abscess and sepsis.

There were 11 postoperative deaths among the 88 patients for an overall hospital mortality rate of 12.5% (Table 4). Four (36%) of the 11 patients died of sepsis and multisystem failure on the 26th, 49th, 60th, and 87th postoperative days. None of these deaths was due to a pancreatic fistula. Two deaths were associated with massive postoperative intra-abdominal hemorrhage requiring re-exploration for control of the bleeding source. Both patients died on the 3rd postoperative day of renal failure and respiratory insufficiency. Two patients died of pneumonia and respiratory failure on the 31st and 48th postoperative days. Two additional patients died of a sudden cardiac arrest on the 7th and 33rd postoperative days. Both of these deaths occurred in patients whose postoperative courses were otherwise unremarkable. The remaining patient died of acidosis and refractory hypotension on the 9th postoperative day. Postmortem examination revealed an infarcted right lobe of the liver, presumably as a consequence of ligation of an aberrant right hepatic artery arising from the superior mesenteric artery. During the recent period, a severe reduction in operative mortality has been observed. Ten deaths occurred during 1969–1980, whereas only one patient died in the recent period for hospital mortality rates of 24% and 2%, respectively ($p < 0.05$).

During the entire 18-year period, the actuarial 5-year survival rate was 18% for the 50 patients with adenocarcinoma of the pancreas (Fig. 1). The actuarial 5-year survival rate was 48% for the 13 patients with negative lymph nodes and 1% for the 37 patients with one or more positive lymph nodes ($p < 0.05$) (Fig. 2). There were no statistically significant differences in the sur-

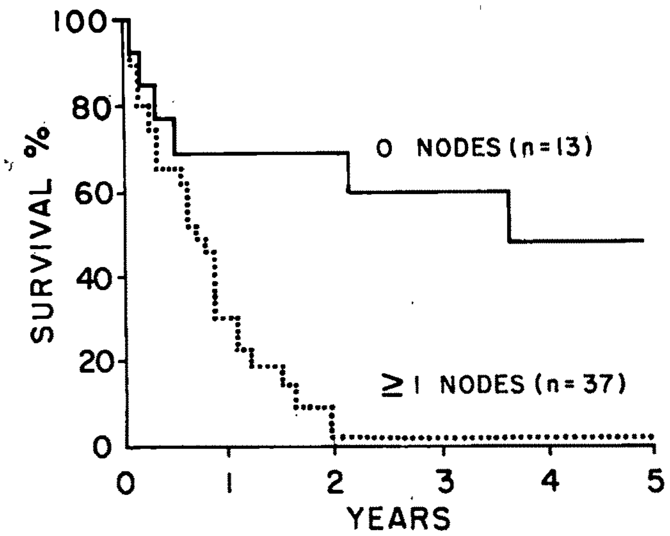

FIG. 2. Actuarial 5-year survival for those patients with adenocarcinoma of the pancreas with and without positive lymph node involvement.

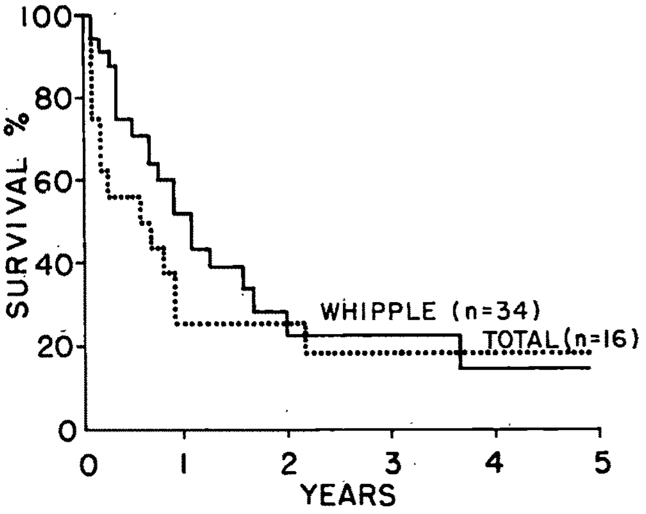

FIG. 3. Five-year actuarial survival for patients with adenocarcinoma of the pancreas managed either by total or partial pancreatectomy.

vival curves between the 34 patients with pancreatic cancer managed by partial pancreatectomy and the 16 patients with pancreatic cancer in whom a total pancreatectomy was performed (Fig. 3). The actuarial 5-year survival rate was 36% for patients with ampullary cancer, 34% for patients with distal bile duct cancer, and 33% for patients with cancer of the duodenum (Fig. 1). Among the 38 patients with nonpancreatic periampullary cancer, the 5-year actuarial survival rate was 23% for the 18 patients with positive lymph nodes and 40% for the 18 patients with no involved lymph nodes ($p = 0.29$).

In comparing the two periods, there were no significant differences in the 5-year survival rates for the 26 patients with adenocarcinoma of the pancreas operated on between 1969 and 1980 and for the 24 patients with pancreatic cancer operated on during the recent period (Fig. 4). Likewise, the 5-year survival rate was similar for the 15 patients with nonpancreatic periampullary cancer operated on during 1969–1980 and for the 23 patients operated on during the recent period.

Thirty-two of 50 patients with adenocarcinoma of the pancreas were operated on 5 or more years ago. Among these 32 patients, six have survived 5 years or longer. Of these six patients, four are alive at 60, 66, 72, and 132 months, respectively. One patient died 76 months after the Whipple resection of metastatic adenocarcinoma of the pancreas, whereas the remaining patient died at 66 months of unknown causes. In comparing the six long-term survivors with the 26 nonsurvivors, there was a trend toward a smaller tumor size among those surviving 5 years or more (2.7 cm *vs.* 3.2 cm, $p = 0.18$). In addition, positive lymph nodes were present in only one of the six (17%) 5-year survivors, whereas 22 of the 26 (85%) nonsurvivors had positive lymph nodes ($p < 0.05$).

Discussion

Over the past decade, a marked decline in hospital morbidity and mortality has been observed for patients undergoing pancreaticoduodenectomy. During the 1960s and 1970s, many centers[11–13] reported operative morbidity and mortality rates of 40–60% and 20–40%, respectively. However, a number of recent clinical re-

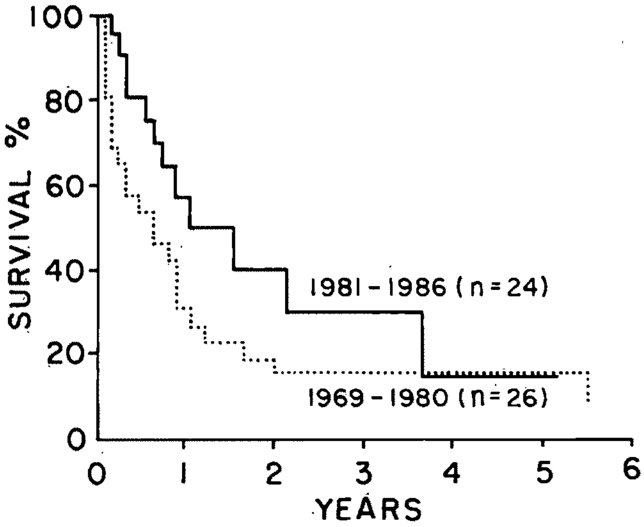

FIG. 4. Actuarial 5-year survival for patients with adenocarcinoma of the pancreas operated on between 1969 and 1980, and between 1981 and 1986. Survival at 5 years is similar for both groups of patients. The difference in survival during the earlier years is explained by the higher operative mortality during the earlier period.

ports[7-9] have documented an operative morbidity rate in the range of 30% and a hospital mortality rate of approximately 5%. A similar decline in hospital morbidity and mortality was noted in the current study. Among the 41 patients operated on during 1969–1980, hospital morbidity and mortality rates were 59% and 24%, respectively. In contrast, among the 47 patients operated on during the recent period, the perioperative morbidity and mortality rates fell to 36% and 2%, respectively.

The decline in operative morbidity and mortality observed during the recent period cannot be explained on the basis of a more select patient population, earlier diagnosis, or extent of disease at the time of operation. Comparison between the two periods revealed no significant differences between the two groups of patients in terms of mean age, race or sex distribution, associated medical illness, or preoperative nutritional status. Likewise, mean duration of symptoms and mean serum bilirubin levels at the time of presentation were similar for both groups of patients. Moreover, the stage of disease as assessed by mean tumor diameter and lymph node status were nearly identical for the two groups of patients.

In comparing the two periods, the number of Whipple resections performed each year at this institution for carcinoma of the head of the pancreas, ampulla, distal bile duct, and duodenum has increased from 3.4 operations per year to 7.8 operations per year. During this same period, a greater number of Whipple resections were performed by fewer surgeons. Between 1969 and 1980, 41 Whipple resections were performed by 22 different surgeons (1.9 operations/surgeon). During the recent period, however, the 47 Whipple procedures were performed by 14 different surgeons (3.6 operations/surgeon) with 50% of the resections performed by one individual. In addition, there has been a considerable change in the type of operation performed during the recent period. Between 1981 and 1986, there were fewer total pancreatectomies (9% *vs.* 39%) and fewer vagotomies (26% *vs.* 76%) performed compared with the earlier period. In addition, a pyloric-sparing Whipple procedure was performed in 14 of 47 patients (30%) operated on during the recent period, whereas a partial gastric resection was performed in all 41 patients operated on between 1969 and 1980. The fact that more operations were performed by fewer surgeons, and that a lesser operation was performed during the recent period, probably account for the shorter operative time (7.8 hours *vs.* 9.0 hours), the decreased mean intraoperative blood loss (1694 mL *vs.* 3271 mL), and the decreased transfusion requirement (3.6 units *vs.* 6.3 units) between 1981 and 1986. These findings suggest that the recent decline in operative morbidity and mortality may be due to fewer surgeons performing more Whipple resections in less time and with less blood loss.

Pancreatic fistula was a common complication in this series, and occurred in 12 of 68 patients (18%) in whom a partial pancreatic resection was performed. Fewer pancreatic fistulas developed during the recent period (14% *vs.* 22%), although this difference did not reach statistical significance. In contrast to other reports,[14,15] there were no deaths that could be directly attributed to the development of a pancreatic fistula in the current series. Neither did the presence of a fistula correlate with the presence of an intra-abdominal abscess, sepsis, or a wound infection. In addition, only one of 12 patients with a pancreatic fistula required reoperation for closure of the fistula at a later time.

Temporary delayed gastric emptying was the most common complication in this series and occurred in 25 of 88 patients (28%). The incidence of delayed gastric emptying was similar among those patients in whom a vagotomy was performed and in those managed without a vagotomy (28% *vs.* 29%). The incidence was also similar in those patients in whom a pyloric–sparing Whipple procedure was performed compared with those managed by a partial gastric resection (29% *vs.* 28%).

The actuarial 5-year survival rate for the 38 patients with nonpancreatic periampullary cancer was 34%. Although the 5-year survival rate (40%) was greater for those patients without lymph node metastases compared with those with nodal involvement (28%), this did not reach statistical significance. The 5-year survival rate for nonpancreatic periampullary cancer in this series was similar to the 30–40% 5-year survival rate reported by others,[15-17] but is less than the 58% 5-year survival rate reported by Grace and Associates[8] and the 70% 5-year survival rate in the series reported by Braasch and co-workers.[9] Surprisingly, the actuarial 5-year survival rate for the 50 patients in the current series with adenocarcinoma of the pancreas was 18%. Six of the 32 patients operated on 5 or more years ago have survived 5 years. Lymph node involvement was very important, with the 5-year actuarial survival rate being 48% in the absence of positive nodes and only 1% when lymph nodes were involved. There was also a trend toward improved survival with a smaller tumor mass. Both findings suggest that earlier diagnosis could have a great effect on overall survival for carcinoma of the pancreas. Of interest, however, is the finding that long-term survival is possible even in patients with positive lymph nodes. One of six long-term survivors with adenocarcinoma of the pancreas was found to have two positive lymph nodes in the resected specimen. This patient is currently alive 66 months after the Whipple resection. There was no difference in survival for those patients managed by total pancreatectomy when compared with those managed by partial pancreatectomy. The improvement in survival seen in this series was present throughout both periods, and a report from this institution[18] covering from 1959–1968, suggests that improved survival for pancreatic cancer was present then. To be certain that our six long-term survivors with pancreatic adenocarcinoma were not in fact patients with more favorable distal bile duct or ampullary lesions, all specimens were re-examined by a pathologist not involved in the original sign-out. All were confirmed as carcinoma of the head of the pancreas. A similar trend toward improved survival for patients with carcinoma of the head of the pancreas has also been noted by the GI Tumor Study group[10] and by Braasch and associates.[9] There is no obvious explanation for this observed improvement in survival for carcinoma of the head of the pancreas.

Acknowledgments

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Survival in 1001 Patients with Carcinoma of the Pancreas

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Among 1001 patients with carcinoma of the pancreas, 23 of 912 patients with exocrine carcinomas, 10 of 46 with ampullary carcinomas, and 21 of 43 with malignant islet cell tumors survived 3 years. Of the survivors with exocrine cancers, there were nine of 97 patients who had curative operation, two had had palliative resections only, and one was an incidental microfocal carcinoma; in the remaining 11 patients a histologic origin in the pancreas was not established. Preoperatively suspected and histologically proven 3-year survivors included six patients with ductal adenocarcinomas, three patients with mucinous cystadenocarcinomas, one patient with acinic cell carcinoma, and one patient with microadenocarcinoma. Only two patients can be considered cured. Tumor size and lymph node status did not correlate with survival. Cystadenocarcinomas comprised 1% of cases but one third of 3-year survivors. Long-term survival in histologically confirmed pancreatic carcinoma is a rare event that cannot be predicted in the individual case.

CARCINOMA OF THE PANCREAS is now fourth among the causes of death from cancer. Over the past 40 years, the incidence in the United States has tripled with an estimated 25,500 new cases in 1986.[1] The University of Chicago experience comprises 1001 cases that include cases of exocrine cancer, endocrine cancer, and carcinoma of the ampulla of Vater. Over 90% of cases are carcinomas of the exocrine pancreas, and it is here that the major problem resides. Although partial or total pancreatectomy may produce significant palliation, both in terms of prolonged survival and freedom from symptoms, there is some doubt as to the number of long-term cures that result. With this in mind, we have studied the records and histologic slides of patients who survived 3 years or longer after operation for exocrine pancreatic cancer at the University of Chicago Hospitals and Clinics between 1946 and 1983, to determine factors that may have influenced the favorable outcome.

Methods

A comprehensive list of all cases indexed as carcinoma originating from exocrine and endocrine pancreas as well as ampulla of Vater between 1946 and 1983 was obtained from the Registry of Neoplastic Diseases of the University of Chicago Hospitals and Clinics. Only patients who survived longer than 3 years were considered and the correctness of their pathologic diagnosis was verified. During this process the pathology of all cases operated for cure and all putative 3-year survivors was reviewed. Carcinomas originating from the endocrine pancreas as well as the ampulla of Vater are not considered in detail in this paper. The diagnosis of "ampullary carcinoma" was restricted to cases where the tumor clearly arose either in the wall of the ampulla or from adjacent duodenal mucosa. Such cases usually showed little or no invasion of the subjacent pancreas. We found that a number of cases originally considered to be carcinomas of the pancreas in reality arose in the ampulla.

Follow-up was available in all cases. Survival times were measured from the date of operation. With rare exceptions the study was confined to examination of the patients' records and review of existing slides, although in a few cases additional recuts and special stains were made. Our data on resectability rate, operative mortality, and long-term survival were compared with those reported in the English literature from 1945 to 1984.

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Results

A total of 1001 patients with carcinoma of pancreas were seen at the University of Chicago Medical Center between 1946 and 1983. These included 43 patients with malignant islet cell tumors and 46 patients with carcinoma arising in the ampulla of Vater. There were 54 putative 3-year survivors, 21 with malignant islet cell tumors, 10 with carcinoma of the ampulla of Vater, and 23 with carcinoma of the pancreas. This paper reports in detail the findings in the latter group of patients, all of whom came from a subset of 766 cases of carcinoma of the pancreas that were treated primarily at our institution. The remaining 146 were initially staged elsewhere and were referred to us for adjuvant therapy. Eighty-nine patients with solid ductal carcinomas, six with cystadenocarcinomas, and one each with acinar cell carcinoma and microadenocarcinoma, respectively, had resection for cure. The extent of these operations is detailed in Table 1.

TABLE 1. *Cases of Carcinoma of the Exocrine Pancreas Operated on for Cure at the University of Chicago Hospitals and Clinics Among 766 Cases Diagnosed and Treated During 1946–1983**

	Solid Ductal Adenocarcinomas	Cystadenocarcinomas and Miscellaneous
Total pancreatectomy	39	1
Whipple	39	3
Distal pancreatectomy	11	4
Total	89	8

* This does not include two of the long-term survivors who were not operated on for cure.

In the larger group of solid ductal carcinomas, the resectability rate was 11.6%. The operative mortality rate was 23.1% for total pancreatectomy and 25.6% for pancreaticoduodenectomy. A total of 67 patients with ductal carcinomas survived the immediate postoperative period. In this group the mean survival was 16.9 months. In 58 patients, the lymph node status was available (this information was lacking in some earlier cases). There was essentially no difference in survival between patients with positive and negative nodes (18.4 *vs.* 17.2 months). In the smaller group of patients with cystadenocarcinomas, the resectability rate was 67%.

The search through the files of the Registry of Neoplastic Diseases yielded a total of 23 3-year survivors (Table 2). Of these, only 11 had a histologically confirmed primary carcinoma arising in the head, body, or tail, and only nine had been operated on for cure. Seven more patients had a histologic diagnosis of carcinoma after exploratory laparotomy and biopsy, but an origin in the pancreas could not be confirmed. In four additional patients there was a clinical diagnosis of pancreatic carcinoma, but histologic proof was lacking, and, in the last patient, a microfocal carcinoma was found incidentally.

The histologically proven survivors fell into two groups: one group comprised six patients with adenocarcinomas of ductal origin and a miscellaneous group comprised one patient with acinar cell carcinoma, one patient with microadenocarcinoma, and three patients with cystadenocarcinomas. The details of these patients are summarized in Table 3. All the adenocarcinomas occurred in older patients (58–72 years, mean: 67 years) with a predominance of females. All were located in the head of the pancreas and measured from 1 to 5.5 cm in diameter. Only the smallest tumor was confined to the head of the pancreas. In four cases, tumor extended into the wall of the duodenum and in two cases the duodenal mucosa was ulcerated. One tumor extended into peripancreatic fat. Histologically all were well-differentiated adenocarcinomas of ductal origin, and one was predominately mucoid. All showed lymphatic invasion, which was obviously perineural in five cases. Three patients had lymph node metastasis. One patient with negative nodes had obvious blood vessel invasion.

In contrast, the cystadenocarcinomas occurred in younger patients (39–54 years, mean: 45 years) and were located in either the head or tail. They tended to be large and ranged up to 21 cm in diameter. Histologically they were all well differentiated. All were mucinous, but two cases showed severe papillary infolding of the epithelium. The single acinar cell carcinoma extended into the wall of the duodenum and peripancreatic fat and had metastasized to seven nodes. The microadenocarcinoma was small and confined to the head of the pancreas, but both perineural lymphatic and blood vessel invasion were evident, and 4 of 21 nodes contained metastases.

The overall 3- and 5-year survival rates of the solid carcinomas were 6.7% (6/89) and 3.4% (3/89), respectively. All long-term survivors were operated on after 1960. Ultimately four of the six patients with ductal adenocarcinomas died of their disease. The two patients still alive without evidence of disease had tumors that measured 1 and 5 cm in diameters, respectively; both

TABLE 2. *Three-year Survivors with Pancreatic Carcinoma at The University of Chicago Hospitals and Clinics During 1946–1983*

	N
Histologically confirmed carcinoma arising in head, body, or tail	11
Histologically confirmed carcinoma but origin in pancreas unconfirmed	7
Clinical diagnosis at laparotomy	4
Microfocal carcinoma found incidentally	1
Total	23

TABLE 3. *Details of Patients with Pancreatic Carcinoma Surviving 3 Years or Longer*

Age/Sex, Diagnosis	Location and Size (cm)	Extent	Invasion Lymph Nodes	Treatment	Follow-up*
F/68, duct cell adenocarcinoma	Head 5.5 × 5.5 × 5.5	Duodenal wall and bile duct	L 3/20	Whipple, RT for recurrence	Died 6.5 years
F/58, duct cell adenocarcinoma	Head 1.0 × 1.0 × 1.0	Confined to pancreas	LP 0/23	Total pancreatectomy	Well 7.25 years
F/62, duct cell adenocarcinoma	Head 3.2 × 3.0 × 2.4	Muscularis of duodenum	LP 5/29	Bypass followed by total pancreatectomy	Died 3.5 years
F/72, duct cell adenocarcinoma	Head 4.0 × 2.3 × 1.6	Peripancreatic fat	LPV 0/15	Total pancreatectomy, postoperative RT and CT	Died 3.7 years
M/67, duct cell adenocarcinoma	Head and body 4.0 × 3.0 × 3.0	Ampulla and ulcerated duodenum	LP 4/44	Total pancreatectomy	Died 3.25 years
M/72, duct cell adenocarcinoma	Head 5 × 5 × 5	Ulcerated into duodenum	LP 0/20	Whipple	Well 12 years
F/54, mucinous cystadenocarcinoma	Tail 21 × 21 × 21	Metastases in ovary, colon, and stomach	— 0/1	Partial pancreatic cystectomy, Salpingo-oophorectomy, RT for recurrence†	Died 3.3 years
F/39, mucinous cystadenocarcinoma	Tail 17 × 17 × 17	Well circumscribed	— 0	Distal pancreatectomy	Recurrence at 14.5 years, died 16.25 years
M/42, mucinous cystadenocarcinoma	Head "Large"	Adherent to duodenum and celiac axis	— 0/1	Biopsy only†	Died 8.75 years
M/41, acinar cell carcinoma	Head 2 × 1.5 × 1	Peripancreatic tissues and duodenum	L 7/32	Total pancreatectomy, postoperative CT	Alive with recurrence 5.1 years
F/30, microadenocarcinoma	Head 2.7 × 2.5 × 1.9	Localized	LPV 4/21	Biopsy, preoperative RT, Whipple and intra-arterial CT	Recurrence 2 years, alive with disease 3.7 years

* All times from date of operation.

† Not considered to be operated for cure.

L = lymphatic, P = perineural, V = vascular, RT = radiation therapy, CT = chemotherapy.

specimens revealed perineural invasion, although in both the lymph nodes were negative. Three of five patients in the miscellaneous group died of their disease and the remaining two patients are alive, but with recurrent disease.

Discussion

Our resectability and mortality rates in the treatment of solid adenocarcinoma of the pancreas are similar to the cumulative experience reported in the English literature, although there is great variability from one series to the other (see Tables 4 and 5). Table 6 lists 5-year survival rates after curative resections for pancreatic ductal adenocarcinomas in recent series; these range from 0–26.7%. Only three series report a 5-year survival rate greater than 10%.[2–4] These favorable long-term survival rates are probably not indicative of progress in the treatment of this disease. Rather, in the study of Kellum et al.,[4] as the authors point out, they only resected "favorable" cases in which tumors measured less than 3 cm in diameter. Another factor that must be taken into account in considering published results is the accuracy of histologic diagnosis and the influence that inclusion of cases of ampullary carcinoma can have on overall survival figures. van Heerden[5] found that among six previously reported long-term survivors, review of the histology revealed that two patients, in reality, had chronic pancreatitis, and one had an islet cell tumor. In our own series (see Table 2) 17% of putative 3-year survivors did *not* have histologically proven carcinoma, and, in a further 29% with histologically proven carcinoma, a definite origin in the pancreas was not established. All of these patients lived 3 years without a resection for cure.

TABLE 4. *Resectability Rate for Solid Adenocarcinomas of the Pancreas Reported in the Literature*

Senior Author	Period	Patients Treated	Patients Resected	Resectability Rate (%)
Morrow[17]	1975–1980	225	39	17.3
Andren-Sandberg[18]	1959–1982	641	90	14
Bjorck[19]	1960–1974	648	62	9.6
Bergstrand[20]	1963–1973	469	44	9.4
Atkins[21]	1965–1974	86	4	5
Nakase[22]	1949–1974	1368	238	17.4
Sato[23]	1960–1976	89	20	22.5
Hermreck[24]	1947–1972	348	50	14.4
Rhoads[25]	1941–1952	83	21	25
Total		3957	568	14.4
Current study	1946–1983	766	89	11.6

Our data also indicate the importance of segregating the ductal adenocarcinomas from the cystadenocarcinomas. In fact, at our institution the 5-year survival rate

TABLE 5. *Operative Mortality after Pancreatoduodenectomy or Total Pancreatectomy for Solid Adenocarcinoma of the Pancreas in Published Series with More than 50 Patients*

			Pancreatoduodenectomy			Total Pancreatectomy		
Senior Author	Period	Total No. of Patients	No. of Patients	Deaths	Mortality Rate (%)	No. of Patients	Deaths	Mortality Rate (%)
Andren-Sandberg[18]	1959–1982	86	1	0	0	85	26	30.6
Herter[26]	1940–1978	75	31	5	16.1	44	10	22.7
van Heerden[15]	1951–1978	51	—	—	—	51	7	13.7
Bjorck[19]	1960–1974	62	62	6	9.7	—	—	—
Cooperman[27]	1940–1978	70	27	3	11.1	43	12	27.9
Nakase[22]	1949–1974	308	308	77	25	—	—	—
Braasch[28]	1957–1974	82	82	11	13.4	—	—	—
Gilsdorf[29]	1951–1970	50	50	9	18	—	—	—
Monge[30]	1941–1962	119	119	25	21	—	—	—
Craighead[31]	? –1956	50	43	22	51.2	7	4	57.1
Total		954	723	158	21.8	230	55	23.9
Current study	1946–1983	89*	39	10	25.6	39	9	23.1

* 11 patients had a radical distal pancreatectomy.

of cystadenocarcinomas is 5 times that of ductal carcinomas. The relatively good prognosis of cystadenocarcinoma is well established.[6,7]

A particularly discouraging feature of our results has been that two thirds of those few patients who survived 3 years, eventually died of their disease. Furthermore, 50% of living patients have recurrent disease. Thus, it appears that the realistic goal of operation must be limited to significantly increased survival, free of symptoms, while maintaining low mortality and morbidity rates. Recently, several series have appeared in which there were no operative deaths,[8,9] emphasizing that in practiced hands this procedure does not carry a risk disproportionate to the long-term gain. Wilson and Block[10] demonstrated that survival after curative resection is significantly lengthened compared with survival after palliative bypass or mere biopsy. Unfortunately, no significant progress in long-term survival has been achieved in four decades. The reasons generally advanced for the poor long-term survival include delay and difficulty in early diagnosis,[11] although the patients in our series who survived longer than 3 years were not generally remarkable for the small size of their tumors. The fact that only 11.6% of our patients could be operated on for cure is in no way different from the general experience.

The location of the pancreas at an anatomic crossroad with drainage to multiple lymph node basins makes a curable lesion an uncommon event. Therefore it is the relative balance of operative mortality *versus* the gain in short-term survival and quality of life that must be considered by each individual surgeon when operating on a patient with ductal adenocarcinoma of the pancreas. Appropriate resections, on the other hand, are clearly indicated for those small subsets of exocrine pancreatic cancers such as cystadenocarcinomas,[7] ampullary tumors,[12,13] and endocrine tumors.[14]

A poorly understood facet of the disease is that of the biologic potential of individual cancer, which appears to be the major factor determining prognosis.[15] In our series, two of 11 survivors were not operated on for cure, yet they survived 3.3 and 8.75 years, respectively. Recently, quantitative tumor DNA analysis has shown that DNA content correlates with the malignant potential of the individual tumor.[16] It remains to be seen if this information will be of clinical usefulness in tailoring the operative procedure for patients with pancreatic carcinoma.

This study underlines the dour prognosis for ductal carcinoma of the pancreas and emphasizes the need to

TABLE 6. *Five-year Survival after Curative Resection for Pancreatic Adenocarcinoma in Series Published Between 1980 and 1984**

Senior Author	Period	No. of Patients	No. Surviving 5 Years	5 Year Survival (%)
Morrow[17]	1975–1980	16	0	0
Kellum[4]	1949–1983	15	4	26.7
Appelqvist[32]	1947–1980	19	1	5.3
Herter[26]	1940–1978	60	3	5
Piorkowski[33]	1967–1978	28	0	0
Huang[3]	1960–1979	19	3	15.8
Hsu[2]	1964–1980	13	2	15.4
van Heerden[15]	1951–1978	44	1	2.3
Bjorck[19]	1960–1974	62	5	8.1
Cooperman[27]	1940–1978	70	5	7.1
Ross[34]	1970–1974	6	0	0
Shead[35]	1970–1976	14	0	0
Total		366	24	6.6
Current study	1946–1983	89	3	3.4

* Calculations do not include hospital mortality.

identify and appropriately treat those other pancreatic tumors whose biologic behavior offers a substantial chance for long-term survival after resection.

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DISCUSSION

DR. HARVEY R. BERNARD (Albany, New York): Data have been collected from all patients discharged from a New York hospital since 1980. Dr. Axelrod, Commissioner of Health for the State of New York, has authorized me to present data pertinent to the matters under discussion this morning.

(Slide) Three points deserve mention. One, these data relative to radical pancreaticoduodenectomy for cancer of the pancreas indicate no statewide improvement in mortality over the period of study.

(Slide) The data are similar in this regard relative to total pancreatectomy for cancer. There is no significant difference from year to year.

Two, practice improved performance. Those hospitals in which the operation was performed four times or more reported a significantly better mortality than did hospitals with less experience. The mortality rate was greater than 30% for hospitals with only one procedure per year. (Slide) Again, the data are similar for total pancreatectomy.

(Slide) This improvement is more clearly demonstrated by the data from 1985 both for the Whipple operation and for total pancreatectomy.

Three, these operations continue to be comparatively rare experiences for a surgeon. The most experienced surgeons in New York State reported only 10 operations: 6 Whipples and 4 total pancreatectomies in 1985.

The average general surgeon in New York State can expect to perform only 2–3 such operations in a 30-year surgical experience with the likelihood of a 30% mortality rate at the current writing.

These operations have been selected for discussion at an upcoming statewide New York Quality Insurance meeting as models of high-risk, high-morbidity, and low-yield procedures, which demonstrates that practice induces improvement.

We must ask ourselves: what are surgeons prepared to do about this?

DR. ANDREW L. WARSHAW (Boston, Massachusetts): I rise mainly to congratulate the authors of both these series and to try to resolve some of what I perceive as a possible conflict between these two papers, one of which is telling us that the Whipple operation is doing much better and the other is telling us how dismal the whole picture is. I believe both are correct and for different reasons.

In our hospital we have also seen a much improved picture, just as Dr. Cameron and Dr. Crist have reported. In my last 88 pancreaticoduodenectomies, including patients up to the age of 86, there have been no postoperative deaths. Nonetheless, if you consider the overall survival of all patients with pancreatic cancer, not just those who can be resected, the world literature shows a total survival rate of 0.4%. What that means is that most patients have metastatic cancer when we first see them. The conflict is therefore not in how we operate on the selected few with cancer in the head who can be resected, but on how we select those patients for operation.

Many patients do not have cancer in the head of the pancreas, and most do not have nonmetastatic disease. Can we stage them in advance, possibly to change approach or even to avoid an operation? In various European series, upwards of 50%, in some cases 75%, of all operations for pancreas cancer are laparotomy and biopsy. I would suggest that in this day and age that is unacceptable.

In our study of patients who apparently had cancer confined to the head of the pancreas, by all standard modalities including CT, angiography, and MRI, we still find that more than 40% have demonstrable gross metastases in the liver or on the peritoneal surfaces at the time of or before the proposed Whipple operation, as demonstrable by laparoscopy. Many of these metastases would undoubtedly have been missed at casual exploration. To my mind this emphasizes the importance of accurate preoperative staging.

In light of that observation, I would like to ask the authors what criteria they use for excluding patients for operation? Will you operate on all patients at any age, or can you identify medical factors that would exclude a patient? We used to exclude patients over 70, but that clearly is not true any more.

In the setting of the poor natural history when the operation is frankly palliative and there are known metastases, is there now a place for totally nonoperative management, such as either endoscopic or percutaneous stenting instead of a bypass? Do we have any evidence that stenting is either better or worse than operative bypass?

Finally, both authors have referred to the presence or absence of positive nodes. There are various reports that either say positive nodes make a difference or they do not. Is this simply the positive node that the pathologist tells you about afterwards, that you did not recognize at the operation, or if you saw grossly positive nodes or biopsy proven positive nodes, would that deter you from doing the Whipple operation? Is the operation so safe now that you would carry it out in obviously palliative circumstances?

DR. JON VAN HEERDEN (Rochester, Minnesota): The two papers just presented, I believe contain both good and bad news. The good news is that pancreatic resection can, in 1987, in experienced hands, be performed with an acceptably low operative mortality and morbidity. The bad news is that by and large, this low operative mortality has not enhanced long-term survival.

Today, at least 90% of patients with ductal adenocarcinoma remain nonresectable, and a 5-year survival rate above 5% is a rarity.

As eloquently outlined by our Chicago colleagues, it is vitally important that the histology of all long-term survivors be re-evaluated, perhaps by an independent pathologist.

The histologic differentiation between a ductal adenocarcinoma, fibrosing pancreatitis, and an islet cell tumor can be notoriously difficult. To our chagrin we found approximately 8 years ago that in a series of six patients who we reported as being 5-year survivors, on re-review three of the six patients did not have ductal cancer; two had pancreatitis and one had an islet cell tumor.

I urge all of us involved in this to have this independent histologic review for all patients who have survived for more than 3 years.

From Dr. Block and his colleagues, I would like to know whether the operative mortality in their experience has dropped in recent years. The operative mortality rate of 23% for total pancreatectomy and 25% for pancreaticoduodenectomy seem extraordinarily high. I wonder too how many surgeons are involved in pancreatic resection at your institution.

(Slide) During 1970–1985, 279 patients had the Whipple procedure at our institution. As you will see by this slide, we are performing an increasing number of Whipple operations, especially if you look at the last 3 years: 1983–1985. This occurs despite our rather conservative attitude towards performing pancreaticoduodenectomy.

We must, however, never lose sight of the overall perspective of patients with this disease entity. This was eloquently outlined by Dr. Connolly. If you look at one recent year at our institution, 1984, of 185 patients with ductal adenocarcinoma, one third never were operated on. Of those who were operated on, an additional 38% had biopsy or bypass alone. A very small percentage had resection.

We have not been able to duplicate the excellent long-term survival as reported by Dr. Braasch and Dr. Cameron.

At our institution, when we compare total pancreatectomy to the Whipple operation for ductal adenocarcinoma, and I emphasize we are talking about ductal adenocarcinoma, in a series of 89 patients with a total and 101 patients with a Whipple, we find an operative mortality rate of 4% for the Whipple, 11% for the total, 3-year survival rate, which is identical, (9%), and a 5-year survival rate that is close to being identical at 6% and 4%, respectively. The mean survival was a dismal 12 months after total pancreatectomy and 16.5 months after the Whipple procedure.

I close, though, with a ray of hope and ask both of the presenters their opinion regarding adjuvant radiotherapy after resection for cure.

(Slide) As you will see in this slide, in a statistically insignificant number of patients with ductal adenocarcinoma who had the Whipple, the total, or distal pancreatectomy followed by radiotherapy, the mean survival was 44 months, and the 5-year survival was 3 of 9 patients, which is 33%.

DR. G. ROBERT MASON (Irvine, California): I would like to congratulate the authors of the Hopkins service on their excellent activity and their excellent results, and in following the marvelous tradition of I. Ridgeway Trimble. As you probably recall, Dr. Trimble was not only one of the first who contributed to the operative procedures for resection, but also for reconstruction, dealing more successfully with the pancreatic remnant by reanastomosing it to the enteric tract.

This has, nonetheless, continued to be one of the major areas of problem for surgeons over the years, and I note that Dr. Cameron also continues to have the pancreatic remnant cause complications not only for fistula but also for abscess and hemorrhage as its major problems.

We have chosen to deal with this in a consecutive series of 25 patients by performing pancreatogastrostomy, and if you would wonder what that is, we will show you a slide or two.

(Slide) Pancreatogastrostomy is performed by a direct mucosal anastomosis to the posterior aspects of the stomach with an incision in the seromuscular layer and a suture of the capsule to the seromuscular layer.

(Slide) This then results in a rather simple enteric anastomosis of the pancreatic duct and stomach, and we have done this both with antrectomy and with pylorus preservation.

(Slide) In animal experiments this has served well as a patent anastomosis for up to 3 months as studied histologically. This has resulted in no morbidity from this particular anastomosis, and in the series of 25 consecutive patients, no mortality for the series of patients.

We have attributed part of our success to pancreatogastrostomy, and we have attributed part of our success to the fact that we are emphasizing the matter of assessing pre- and postoperative nutrition, the use of H2 blockers, the use of critical care monitoring, and the use of percutaneous drainage of fluid collections.

In the success rate that Dr. Cameron notes in his operative procedures, I would wonder if these latter items have contributed also to his success as they certainly were not available in the earlier years of his series.

DR. MARTIN S. LITWIN (New Orleans, Louisiana): I am pleased to have the opportunity to discuss these two excellent papers.

The treatment of adenocarcinoma of the pancreas is one of the last great surgical therapeutic frontiers. It provides surgeons with the opportunity to care for a disease that remains a therapeutic enigma. For those of you who work in this area, you know that Dr. Bernard's conclusion is a correct one; *i.e.*, practice does, indeed, make perfect, but it is perhaps a little more difficult to practice here than in other areas simply because of the deep-seated location of the disease. There is no doubt in my mind that the seat of the soul is in the pancreas. Cardiovascular surgeons deal with life in their hands, but general surgeons who operate on the pancreas deal with the soul.

In the last few years the technique of total intravenous hyperalimentation has allowed us to improve considerably operative morbidity and mortality for these patients. One of the most difficult tasks that a surgeon has when dealing with a patient who has adenocarcinoma of the pancreas is to do nothing until the patient has been adequately prepared for surgery with adequate nutrition. Intravenous hyperalimentation in the preoperative period for a minimum of 5–7 days and continuing into the postoperative period has allowed us to approach figures for morbidity and mortality similar to those presented by Dr. Cameron this morning.

The use of intravenous hyperalimentation allows a debilitated patient to be restored toward a state of positive nitrogen balance. In the postoperative period his ability to heal suture lines and to fight infections is vastly improved, and pancreatic fistulas have become almost unknown.

I would like to pose a question for both Drs. Block and Cameron. Were any of your patients treated with intravenous hyperalimentation before surgery, and if so, how did those compare with others who were not so treated?

DR. GEORGE L. NARDI (Boston, Massachusetts): I enjoy these hearty perennials on the pros and cons of surgery for pancreatic cancer, and I rise to make a couple of comments. I have no slides. I just wanted to tell of an experience of 20 years ago when I was reviewing mortality and survival in this type of surgery.

It disturbed me, being at the Massachusetts General Hospital, to see that the Lahey and Mayo Clinics both had much better results than we did. Their mortality was one third and their 5-year survival, 2 or 3 times what ours was.

I found a simple answer. We had about 16 surgeons doing our Whipple operations, whereas they had four and two, and there was a straight line correlation. We also found that our operability or resectability was 20% and theirs was less than 10%. It was apparent that mortality correlates with the number of surgeons doing the procedure and survival correlates with selection of patients.

I ask Dr. Cameron his operability or selection rate.

The last comment to set the record straight: there was an old paesano of mine named Codivilla who did a pancreatic resection back before the turn of the century for sarcoma. The patient survived nicely for 21 days, but unfortunately, died of sepsis.

DR. JOHN BRAASCH (Burlington, Massachusetts): I have enjoyed these two papers. They might represent the Ying and the Yang of the subject or the highball and the lowball, and I believe it is fair to make Dr. Cameron fair game because he is the highball. Let us look at his two major premises. First his excellent morbidity and the mortality. I believe that that has been confirmed from a number of institutions in this country and abroad. For instance, Ron Tompkins at UCLA has reported his low mortality. The Mayo Clinic has, as have we at the Lahey Clinic. Now Dr. Cameron and the MGH have from this country. There are two groups in Germany who have likewise had very low morbidity and mortality after the Whipple procedure.

The second area in which we might examine Dr. Cameron's results is that of the actuarial survival.

(Slide) I have always been suspicious of actuarial survivals and especially I was suspicious of the figures that I presented 1 year ago. This is the slide that I used.

Since these data were accumulated for the slide, we have had another 1.5 years of follow-up, and there has been a dropoff in survival of bile duct adenocarcinomas. That is going to end up, it looks like, at a 5-year survival rate of around 45% instead of about 65%.

Ampullary carcinomas are going to drop off, and it looks like it is going to be 50–60% instead of 70%. However, in a small series of adenocarcinomas of the pancreas, our two survivors (20%) out of this rather small group are still living at 61 months and 84 months without evidence of disease. These have been re-evaluated, and these, indeed, are adenocarcinomas, both node negative and are the usual kind that you see.

Finally, I would like to leave one more thought with you as has been suggested by other discussants. One question is: should we be training all general surgeons to do this procedure, and secondly, if we do train them, should they all be allowed to do the procedure if they choose?

DR. ALEXANDER J. WALT (Detroit, Michigan): John Braasch has just superseded me. I was going to comment that for most general surgeons, performing a Whipple in their surgical lifetime has long represented something of a trophy to be achieved, a surgical scalp. Dr. Axelrod, the health commissioner, probably had the information about the results in New York State yesterday. We have the results of two large series presented here today. The AARP will have the same results tomorrow and the science writers the day thereafter. Knowledge of such data carries at least two important implications. Firstly, do we now feel strongly enough in light of all these data to advocate the regionalization of the Whipple operation since it carries this high mortality and overall poor results, especially in institutions where there is little experience and where there is no opportunity for a significant experience to be acquired? Secondly, as individual chiefs of surgery in our various hospitals, do we have the will and the support to restrict the privilege for this operation to a small group of surgeons who have proven their ability to do the operation safely and well and to whom we will channel a sufficient number of cases to ensure high quality in the care of the patient?

DR. JOHN L. CAMERON (Closing discussion): I thank the many discussants for their comments and questions.

We, as I believe everyone else, when we first saw our data were suspicious that perhaps we were calling lesions carcinoma of the head of the pancreas that were more favorable distal bile duct or ampullary lesions. Therefore, we took our six 5-year survivors among those 32 patients with carcinoma of the head of the pancreas who were treated 5 or more years ago and had them re-reviewed by a pathologist at Hopkins who had not been involved in their initial signout. Pathologists are no different than surgeons. This pathologist would have loved to have found that these had been mistakingly signed out as carcinoma of the head of the pancreas, but on re-review they were all confirmed to be carcinoma of the head of the pancreas. I believe Dr. van Heerden's comments are appropriate and we would be happy to have these six patients reviewed by outside pathologists.

We, as many others, are somewhat suspicious of actuarial survival data. However, when we look at our 32 patients with cancer of the head of the pancreas who were operated on 5 or more years ago, there are six 5-year survivors for an actual 5-year survival rate of 19%, which is similar to our actuarial 5-year survival rate for all 50 patients of 18%. Therefore, we are convinced that the survival is real and that all patients indeed did survive carcinoma of the head of the pancreas.

The studies from the University of Chicago and the one from Hopkins are really not comparable. Whenever you look at something over four decades, it is always difficult for me to understand what the figures mean, and I believe that the two studies cannot be compared. I believe they were not looking for recent trends, which is what we were looking for. I believe they have the data to look at the same aspects of the disease and its management that we have, and perhaps they will or have already done it.

In answer to Dr. Warshaw, up until several years ago, we were restricting the Whipple to patients 70 years of age or less. But because everybody was surviving, we felt perhaps we were not extending it to enough patients, so now there really is no age limit among the patients we have done. We have one patient who is 84 and another who is 90. The 90-year-old patient was treated just a couple of weeks ago and recently left the hospital.

The presence of positive nodes was used to exclude a patient from being a candidate for a Whipple procedure for carcinoma of the head of the pancreas. However, we have one 5-year survivor who had two positive nodes; therefore, we would not exclude such a patient from a Whipple procedure today.

I believe there are some patients with carcinoma of the head of the pancreas who should not be operated on, but have their biliary tree decompressed with an endoprosthesis placed either endoscopically or percutaneously. In those patients with other diseases and illnesses that are unable to tolerate a Whipple, I believe we have nothing to offer them over a biliary decompression, which can be done nonoperatively. In addition, in those patients with widespread disease, I believe we offer them very little with operative intervention.

I believe one extension of our study is: should this operation ever be done as a palliative procedure? That has been looked at in the past, but it was looked at when one of every four patients we operated on would die. Now that it can be done with little hospital morbidity and mortality, I believe we have to at least consider whether or not it should be offered to a patient as a palliative procedure.

I believe Dr. van Heerden brings up a good point in terms of adjuvant therapy for patients with carcinoma of the head of the pancreas, and I believe that is the area where future hope rests for even improved survival. The GI Tumor Study Group reported their data in 1985 and in a series of about 40 patients, in the one half that were treated with adjuvant radiotherapy and chemotherapy, mean survival doubled and there was a 5-year survival rate of 15%. Our patients who survive a Whipple procedure and are discharged from the hospital with carcinoma of the head of the pancreas also receive adjuvant radiotherapy and chemotherapy.

In answer to Dr. Mason, we had 12 fistulas among our 88 patients. However, unlike other series, none of the 12 patients with pancreatic cutaneous fistulas died. Also, the fistulas did correlate with wound infections, postoperative sepsis, or the development of an intra-abdominal abscess. Therefore, for unclear reasons they were not the life-threatening complication in our series as in others. Eleven of the 12 closed spontaneously. Only one patient had to be operated on for a persistent fistula.

Few of our patients had preoperative TPN. One of the reasons the review extended back to 1969 was because that was when we first had a TPN team in our hospital and, therefore, it was available during the entire period. Many of the patients in whom complications developed after operation had TPN administered, but not before operation.

In answer to Dr. Nardi, we are not certain what our resection rate is now, but that also seems to have increased significantly, and we have the impression that it is now about 30%. We have the numerator, how many Whipples we have done during the last 20 years, and we are now looking up the denominator to see what the resectability rate is.

Again in answer to Dr. Braasch, actuarial survivals are somewhat of a risk when you rely on them too heavily. But both the real and actuarial survival rates are 18 and 19% for carcinoma of the head of the pancreas.

Dr. George E. Block (Closing discussion): It is my privilege to close Dr. Connolly's and Dr. Dawson's presentation, and I thank all the discussants for their wide-ranging and spirited discussion.

It is tempting to look at the two presentations on cancer of the pancreas today and immediately try to compare them. Although they are not really comparable, one might gather from the presentations that the surgeons in Chicago do not know how to treat the disease and that the surgeons in Baltimore do not know what disease they are treating. Such conclusions are obviously unfair.

It is worthwhile to emphasize that based on a critical review of our own experience, ony 4% of our patients had an ampullary carcinoma. Approximately one third of the patients in Dr. Cameron's series had periampullary or ampullary carcinoma. The survival rates from ampullary carcinoma in the two institutions are comparable, indicating that we are doing similar "cancer operations."

As far as the question of palliation is concerned, it is a nonsequitur. If we accept a 15% cure rate, a 5% cure rate, a 2% cure rate, or 0.2% cure rate, then by definition the operation is palliative. We must look at the operation for ductal carcinoma of the pancreas just as we do at resections for cancer of the esophagus. The majority of the operations are palliative.

To answer some of the discussants specifically, as time goes by our resectability level stays the same, about 14%. Our aggressiveness, however, decreases.

Since the advent of percutaneous decompression, many of my colleagues and I have adopted a philosophy that not all patients with cancer of the pancreas have to die with a scar on their abdomen. By using such diagnostic modalities as CT scanning, NMR, etc., we now can choose slightly better, but not perfectly, those patients who will obviously not benefit from operation.

Concerning radiation, our experience with postoperative radiation has not been favorable. The effect of intraoperative irradiation of these patients has yet to be determined.

Our experience does parallel Dr. Axelrod's experience in New York. As far as Dr. Litwin's comments are concerned, I do not believe we looked at TPN because this study goes back into the 1940s. From my own experience, however, I do not believe that we can achieve anabolism in 5 days. I would rather use parenteral alimentation in the postoperative period to carry these patients over a period of prolonged starvation. Although this does seem to help, we do not have objective data.

I certainly agree with Dr. Braasch's and Dr. Walt's suggestions that this is not an "every man" operation. I do not know if I can embrace the regionalization concept, however. From our experience it appears that today the majority of pancreatic resections in Chicago are attempted by surgeons familiar and skilled in the procedure. From Dr. Moossa's contributions and our own experience, our recent operative mortality rate approaches that of Dr. Braasch and Dr. Cameron.

We have not yet reached the 5% mortality rate, but we are hovering around 7% and it does improve with the learning curve of the surgeon.

In one final note I emphasize that the point of our paper is that the histologic diagnosis is the crux here and that we did not use actuarial survival. We determined actual survival. All of these patients were followed until death or 5 years or more.

I am a bit confused by actuarial survival. Therefore I asked our statistician before I came here to review the concept of actuarial survival with me. He told me that I would not understand it, but to clarify he explained that according to actuarial survival, Andy Warhol is still alive.

Angiostatic Steroids

Method of Discovery and Mechanism of Action

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A new class of steroids has been found that inhibits angiogenesis in the presence of nonanticoagulant heparin. Tetrahydrocortisol is the most potent of the naturally occurring angiostatic steroids. It is a metabolite of cortisone that circulates in the blood, appears in the urine, and was previously believed to be biologically inactive. Both the plasma form and the urinary form are antiangiogenic. The mechanism of action of these steroids depends on their ability to specifically alter basement membrane turnover in growing capillary blood vessels. These steroids represent a prototype of angiogenesis inhibitors that may find potential therapeutic use as adjuncts to anticancer therapy, and in diseases dominated by abnormal neovascularization, *i.e.*, angiogenesis-dependent diseases.

ENDOTHELIAL CELLS, which line the entire vascular system, are relatively quiescent compared with other cell types. Intestinal mucosal cells, for example, undergo billions of cell divisions every day, and the entire lining of the intestine is replaced or "turned over" in 3 days. The turnover time of bone marrow cells is approximately 5 days. In contrast, the turnover time of vascular endothelial cells is measured in years.[1] During the growth of new capillary blood vessels, however, vascular endothelial cells are capable of rapid proliferation with turnover times of a few days. When this process of angiogenesis occurs normally or physiologically, it seems to be almost unique to females. Physiologic angiogenesis occurs during ovulation, after menstruation, and during development of the placenta. Angiogenesis is rarely observed in males unless it is of pathologic origin. Thus, a male may live an entire lifetime without angiogenesis unless he is wounded or a disease develops dominated by neovascularization.

Pathologic Angiogenesis

It is becoming clear that unabated capillary blood vessel growth can be the basis of devastating diseases that occur in both males and females. These diseases, previously believed to be unrelated, can now be considered "angiogenesis-dependent diseases," and can be found in almost every branch of medicine and surgery. They generally share two characteristics in common: (1) an abnormality of capillary blood vessel growth as a principal pathologic feature, and (2) the possibility that therapeutic control of the abnormal capillary growth would ameliorate or eliminate other manifestations of the disease. Diabetic retinopathy, retrolental fibroplasia, and neovascular glaucoma are some examples of pathologic neovascularization. In fact, neovascularization is one of the most common causes of blindness worldwide. Excessive neovascularization can also damage other tissues. Cartilage in the arthritic joint may be destroyed by neovascularization. Rapidly growing hemangiomas often disfigure babies. Excessive neovascularization in the skin is a dominant feature of psoriasis.

The most persistent and intense angiogenesis is associated with tumor growth.[2,3] There is accumulating evidence that progressive tumor growth is dependent on angiogenesis and that an increase in tumor cell population depends on new capillary blood vessels that converge on the tumor.[4,5]

Tumor angiogenesis seems to be initiated by diffusible angiogenic factors released by the tumors themselves[3] as well as by cells such as macrophages,[6] which tumors

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recruit.[6–8] At least four angiogenic factors have been isolated from both tumors and normal tissues. These four factors have been completely purified, the amino acid sequence of their proteins determined, and their genes cloned (for review see reference 2).

Angiogenesis Inhibitors

In 1972, we proposed the idea that "antiangiogenesis" could be a potential therapeutic approach against solid tumors.[9] No angiogenesis inhibitors were known at that time, however.

The first angiogenesis inhibitor was discovered in cartilage,[10–13] but has not been completely purified nor is it available in sufficient quantity for antitumor testing in animals. Protamine was also shown to be an angiogenesis inhibitor,[14] but toxicity increased with prolonged administration. Recently, we described a new class of steroids that have the inhibition of angiogenesis[15–17] as their principal function.

The elucidation of this new steroid activity resulted from a previous inquiry about the role of heparin in angiogenesis. We observed a 40-fold increase in mast cells at the site of a tumor implant in the chick embryo, just before new capillary sprouts converged on the tumor.[18] Increased mast cells also had been found in human hemangiomas during the proliferative phase of these vascular tumors.[19] Mast cell heparin stimulated locomotion[20] of endothelial cells *in vitro*[21] and significantly increased the rate of tumor-stimulated capillary growth *in vivo*.[14] On the basis of these results, heparin was used in the chick embryo chorioallantoic membrane bioassay for angiogenic factors because it reduced the time required for a positive angiogenic response from 3 days to 1 day.[14,22,23] The "heparin-enhanced" chick embryo bioassay set the stage for the discovery of steroids that could inhibit angiogenesis.

The chick embryo chorioallantoic membrane has served as a useful bioassay for angiogenic activity during the past decade.[24,25] Originally, a window was made in the eggshell, and angiogenic factors dissolved in a pellet of methylcellulose were applied to a 9-day chorioallantoic membrane. A positive angiogenic response was recorded if new capillaries and small venules converged on the implanted pellet in a spokewheel pattern. (This bioassay was subsequently improved by removing the embryo from its shell on day 3 and using the 6-day chorioallantoic membrane as the testing site for angiogenic substances.[5,26] A problem with the former method was that eggshell particles occasionally fell on the chorioallantoic membrane and caused inflammatory neovascularization. Pretreatment of the chorioallantoic membrane with cortisone or hydrocortisone abolished the inflammatory reaction. Fortunately, these steroids did not suppress angiogenesis induced by tumor extracts.

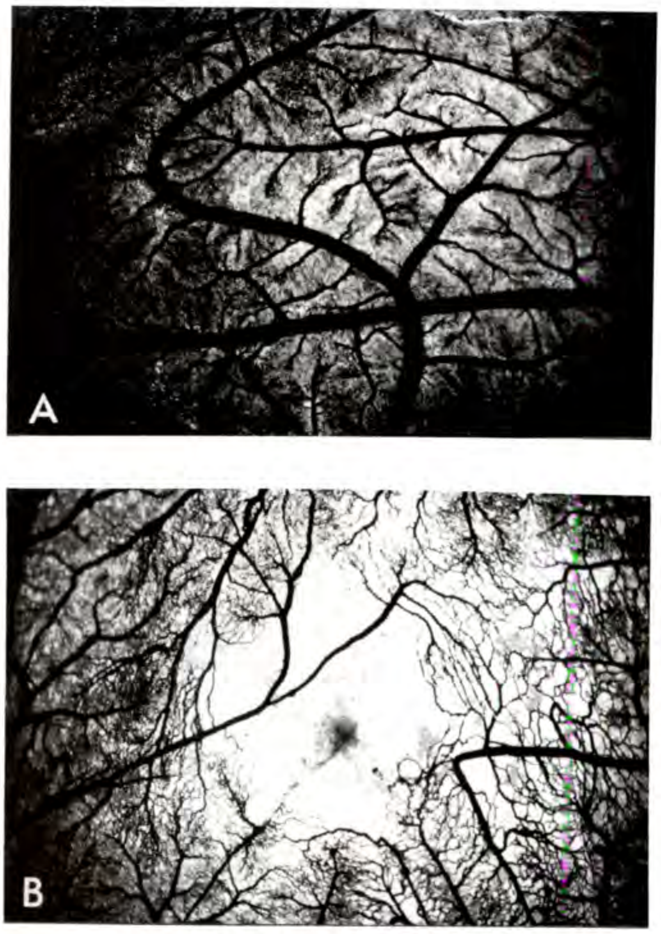
A New Class of Angiogenesis-inhibiting Steroids

Tumor angiogenesis was inhibited, however, when cortisone and heparin were applied together.[15] Furthermore, an avascular zone appeared in the chorioallantoic membrane surrounding the methylcellulose pellet containing the heparin–steroid mixture. Histologic sections showed that growing capillaries had actually regressed, leaving a hole in the membrane covered only by a layer of ectoderm and endoderm. Nongrowing capillaries and larger vessels were not effected. This unexpected antiangiogenic activity was independent of the anticoagulant activity of heparin. Nonanticoagulant fragments of heparin produced by enzymatic cleavage[15] or chemical synthesis[16] were more potent than whole heparin. It was thus possible to construct dose-dilution curves to determine the optimal concentrations of heparin and steroid (Figs. 1 and 2). As the concentration of hydrocortisone was increased beyond an optimum level (*e.g.*, 50–60 μg/10 μL), antiangiogenic activity diminished, generating a bell-shaped curve (Fig. 2).

In our first report of this new phenomenon[15] we were puzzled by an apparent paradox. Dexamethasone plus heparin had little or no antiangiogenic activity when tested at the concentrations where cortisone and hydrocortisone (in the presence of heparin) were maximally effective. Yet, dexamethasone is a synthetic analogue of hydrocortisone with approximately 25–30 times its glucocorticoid (anti-inflammatory) activity. During the year after this report, we completed dose-dilution curves for a variety of other natural corticosteroids. We noticed that they also produced bell-shaped curves, *i.e.*, the highest antiangiogenic activity for a given steroid often occurred at a lower concentration than the highest concentration tested.[16,27]

When dexamethasone was re-examined at concentrations far below effective doses for hydrocortisone, there was a sharp peak of antiangiogenic activity at 2 μg (with heparin), almost 1/25th the optimum dose for hydrocortisone. Dexamethasone, however, showed no antiangiogenic activity from 3–200 μg. In fact, concentrations above 100 μg were toxic, and 200 μg of dexamethasone killed all embryos. The eventual solution to the paradox lay in the fact that dexamethasone produced its own bell-shaped curve of antiangiogenic activity with an optimum dose of 2 μg instead of the 50–60 μg optimum level for hydrocortisone.

Before this paradox was solved, we had begun to explore an alternate possibility. The apparent lack of an-



FIGS. 1A and B. Normal (*A*) and angiostatic steroid-treated (*B*) CAMs injected intravascularly with India ink/Liposyn mixture (see below) on day 8. *A.* Normal 8-day CAM contains a continuous vascular network beneath its surface ectoderm. *B.* CAM exposed to a methylcellulose sustained-release polymer containing 6a-fluoro-17,21-dihydroxy-16b-methyl-pregna-4,9,(11)-diene-3,20-dione (Upjohn, Kalamazoo, MI) (50 μg) and heparin (50 μg) for 2 days. Note the avascular zone within the center of the view, which is free of capillaries, although a larger vessel remains intact. The semiopaque methycellulose disc can be seen in the central portion of the zone. These avascular zones were used to generate dose-dilution curves for heparin–steroid combinations (see Fig. 2). India ink was injected through a 33-gauge needle into the major artery supplying the chorioallantoic membrane of chick embryos. A mixture of India ink 1:6 with a lipid emulsion (10% Liposyn II, Abbott Laboratories, North Chicago, IL), gave the most uniform distribution of ink into the finest capillaries. The chorioallantoic membranes were then fixed with formalin and photographed from above.

tiangiogenic activity by the potent glucocorticoid dexamethasone suggested that the antiangiogenic activity of hydrocortisone and cortisone (in the presence of heparin) could be independent of glucocorticoid activity. This hypothesis was tested by substituting 11alpha-hydrocortisone (epicortisol) for hydrocortisone (Fig. 3). Epicortisol is the biologically inactive stereoisomer of hydrocortisone.[28] The alpha position of the 11-hydroxyl group eliminates glucocorticoid and mineralocorticoid activity. Epicortisol inhibited angiogenesis and caused capillary regression (in the presence of heparin) as had hydrocortisone, although epicortisol was slightly less active than hydrocortisone on a molar basis.[16,27] At this writing, inhibition of angiogenesis is the only known biological activity of epicortisol.

Structure–Activity Relationships of Steroids that Inhibit Angiogenesis

A search was initiated for other corticosteroids in which antiangiogenic activity might be dissociated from glucocorticoid and/or mineralocorticoid activity. More than 100 corticoids and related compounds were tested for antiangiogenic activity. Each steroid was dissolved or suspended in the presence and absence of heparin, in 10 μL of methylcellulose (0.45% in distilled H_2O) and pipetted onto a Teflon rod of 2-mm diameter.[16] The droplet was air-dried (in a laminar flow hood) to a disk of 2-mm diameter and implanted on the 6-day chorioallantoic membrane of the shell-less chick embryo cultured in a humidified incubator at 37 C and 3% CO_2. An optimum heparin concentration was found to be 50 μg. A dose-dilution curve was generated for each steroid (1–200 μg) in the presence of heparin. Each steroid was also tested alone at the optimum and maximum doses. At least 20 embryos were examined for each steroid concentration. The endpoint for angiogenesis inhibition was an avascular zone of 4-mm diameter or larger 48 hours after implantation of the methylcellulose pellet. A mixture of hydrocortisone-21-phosphate (Sigma, St. Louis, MO), 60 μg/10 μL, plus heparin (Hepar Inc., Franklin, OH), 50 μg/10 μL, was used as a positive control.

An antiangiogenic index was determined as the percentage of embryos with avascular zones (4-mm or

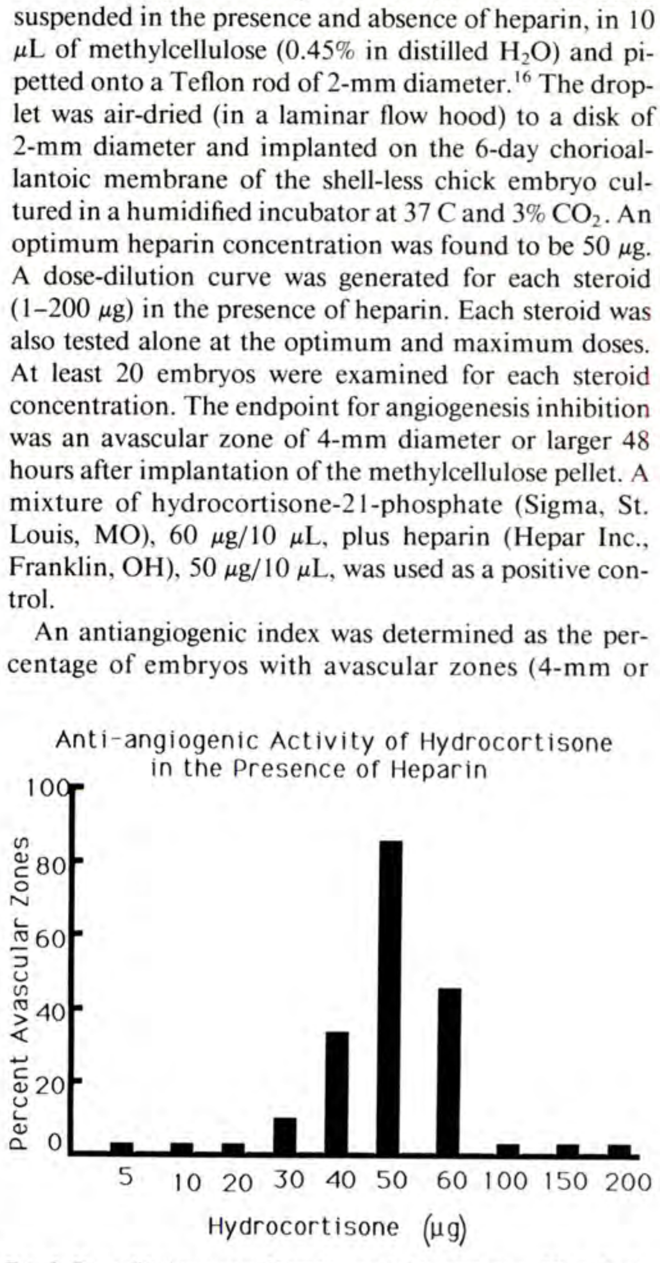
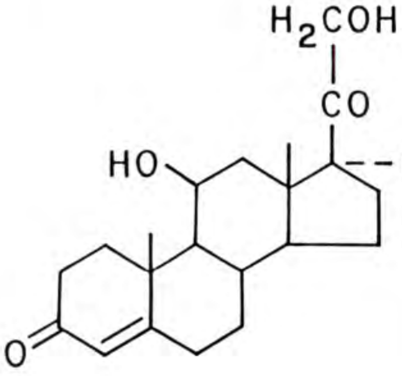
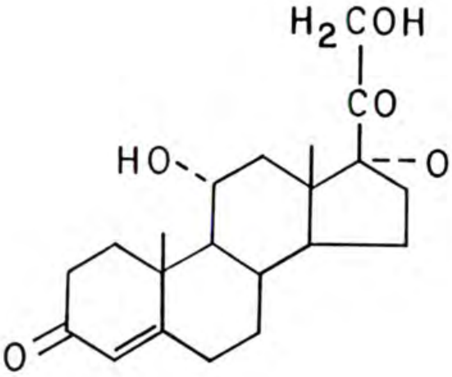


FIG. 2. Dose-dilution curve. Heparin was held constant at 50 μg. Each bar represents 20 embryos.



HYDROCORTISONE



11a-EPIHYDROCORTISOL

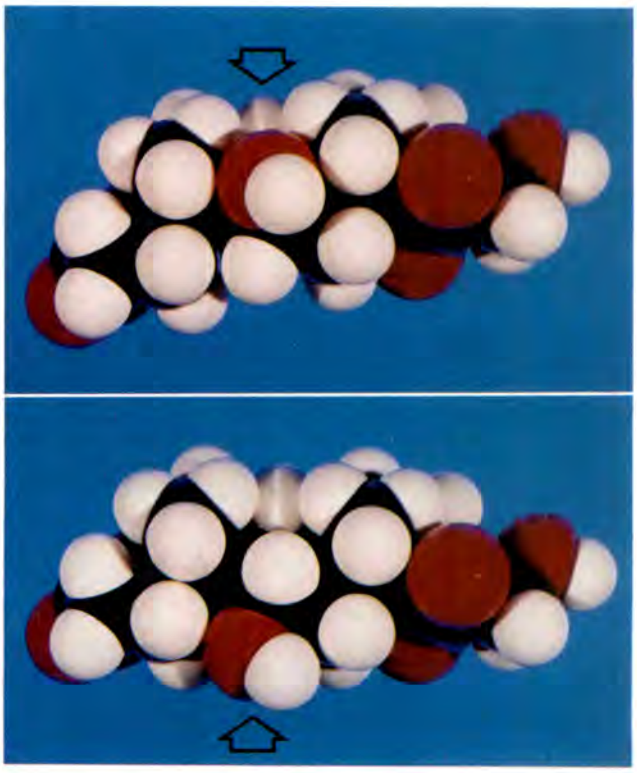


FIG. 3. Hydrocortisone and its biologically inactive stereoisomer, 11-alpha-epihydrocortisol differ only by the position of the 11-hydroxyl (arrow) in the plane of the molecule. The 11-hydroxyl lies above the plane in hydrocortisone (beta position) and below the plane in 11-alpha epihydrocortisol (alpha position). 11-alpha epihydrocortisol retains only angiostatic activity, and lacks all of the other functions of hydrocortisone.

greater diameter) at the most active dose, divided by the most active dose expressed in micromoles (for example, the molecular weight of hydrocortisone is 362.5. The most active dose was 60 μg. 60/362.5 = 0.166 μmol. Its antiangiogenic index was 60/0.166 = 361). The antiangiogenic indices of each compound were then compared.

Antiangiogenic Activity of Natural Steroids and Related Compounds

Of the naturally occurring corticosteroids, tetrahydrocortisol was the most potent inhibitor of angiogenesis. Its relative potency is shown in Table 1.

Tetrahydrocortisol lacks the 4,5 double bond in its A ring (Fig. 4), and, for this reason, lacks all of the known functions of cortisone. In fact, it is one of the major metabolites of cortisone[29] previously believed to be without biological activity. Steroids are mainly inactivated in the liver by the enzymatic reduction of the 4,5 double bond in the A ring forming the dihydro derivative (Fig. 4). The dihydro derivative is converted to a

TABLE 1. *Relative Antiangiogenic Potency*

Compound	Percent Potency
Tetrahydrocortisol	100
17a-hydroxyprogesterone	56
Hydrocortisone	51
11a-epihydrocortisol	14
Cortexolone	12
Corticosterone	12
Desoxycorticosterone	8
Testosterone	3
Estrone	2
Progesterone	0
Pregnenolone	0
Cholesterol	0

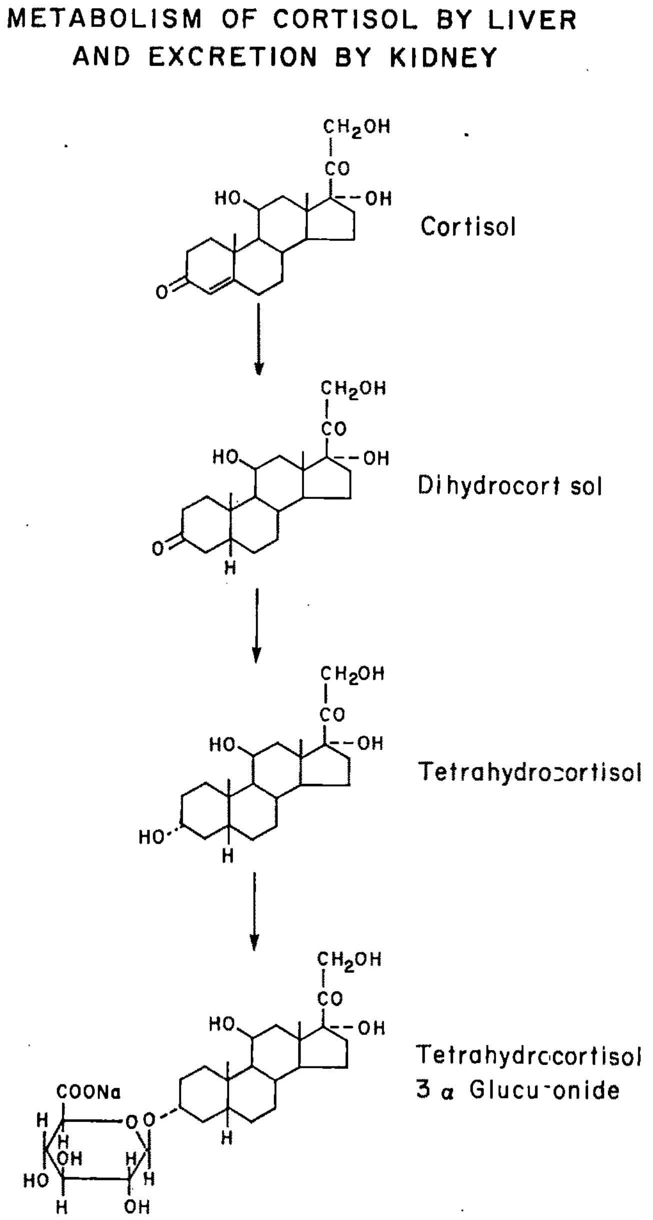


FIG. 4. The metabolic pathway by which cortisone is inactivated in the liver and excreted in the kidney. Tetrahydrocortisol, previously believed to be an inactive metabolite, is now known to be highly angiostatic (in the presence of a heparin fragment). Its urinary derivative, tetrahydrocortisol-3-glucuronide, is also a very active angiogenesis inhibitor.

tetrahydro derivative by the enzymatic reduction of the 3-oxo group to a 3-hydroxyl group. This compound is lipid soluble. It is then conjugated with glucuronic acid to become a water-soluble product that can be excreted by the kidney.[29]

Thus, tetrahydrocortisol represents a steroid with pure antiangiogenic activity independent of either glucocorticoid or mineralocorticoid activity. It defines a new class of steroids that we have named "angiostatic steroids." Cortexolone and 17a-hydroxyprogesterone are other examples of angiostatic steroids that lack gluco- and mineralocorticoid activities. When the structures of the compounds in Table 1 are taken together with structures of a variety of synthetic steroids (not shown) that we have tested, four rules predict antiangiogenic activity: (1) the 11- and 21-hydroxyl groups can be removed without significant loss of angiostatic activity; (2) the 17-hydroxyl group is essential, because its removal reduces antiangiogenic activity by approximately 76% of the activity of hydrocortisone.[16] Thus, maintenance of antiangiogenic activity is governed mainly by structural components on the D ring of the pregnane nucleus; (3) reduction of the A ring increases antiangiogenic activity by almost twice that of hydrocortisone; and (4) pregnenolone, a derivative of cholesterol and a general precursor for the biosynthesis of adrenal steroids, is inactive, as are structures such as progesterone, which lack all three hydroxyl groups (11-, 17-, and 21-).

Recently, it has been found that glucuronic acid can be synthetically conjugated to the 3-hydroxyl position of tetrahydrocortisol and that it retains very high antiangiogenic activity in the presence of heparin.[30] The conjugated compound is water soluble. This is the first demonstration of a biological activity for this urinary metabolite of hydrocortisone.

Inhibition of Tumor-Angiogenesis by an Angiostatic Steroid

Angiostatic steroids can inhibit tumor-induced angiogenesis when used at pharmacologic doses in the presence of exogenous heparin. This is most clearly demonstrated by inserting V2 carcinoma into a corneal pocket of a rabbit eye, a method that has been previously described.[14] A 1-mm^3 tumor implant is placed 2 mm from the limbal edge of the cornea. New capillaries grow toward the tumor in a dense pannus and increase their length at an average of 0.2 mm per day. A 1-mm pellet of ethylene vinylacetate copolymer[13] is impregnated with heparin and $\Delta^{9(11)}$ 11-deoxycortisol and inserted into the cornea between the tumor and the vascular bed. Control eyes contain either an empty polymer or a polymer with heparin or steroid alone (Figs. 5A–C). Capillary growth is almost completely inhibited only in the corneas implanted with both heparin and the angiostatic steroid.

A Proposed Physiologic Role for Angiostatic Steroids

Tetrahydrocortisol, when administered at pharmacologic doses with exogenous heparin, can induce capillary regression in the growing vessels of the chick embryo, and at the doses used, can inhibit but not regress capillary growth induced by intracorneal tumor. It is unclear whether circulating tetrahydrocortisol has a physiologic role. One can speculate that it may act synergistically

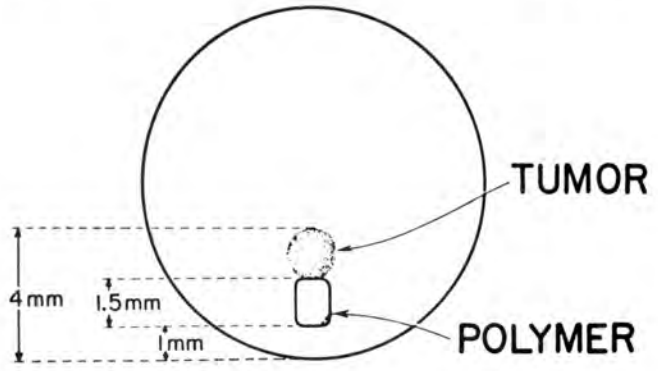


FIG. 5A. Diagram of position of intracorneal tumor implant and polymer pellet containing steroid–heparin mixtures.

with the heparin-like molecules that are known to be on the surface of the endothelial cell[31] and embedded within its basement membrane, as well as within nearby mast cells, to prevent capillary growth under normal conditions. We have obtained some experimental evidence to support this hypothesis. Desulfation is one of

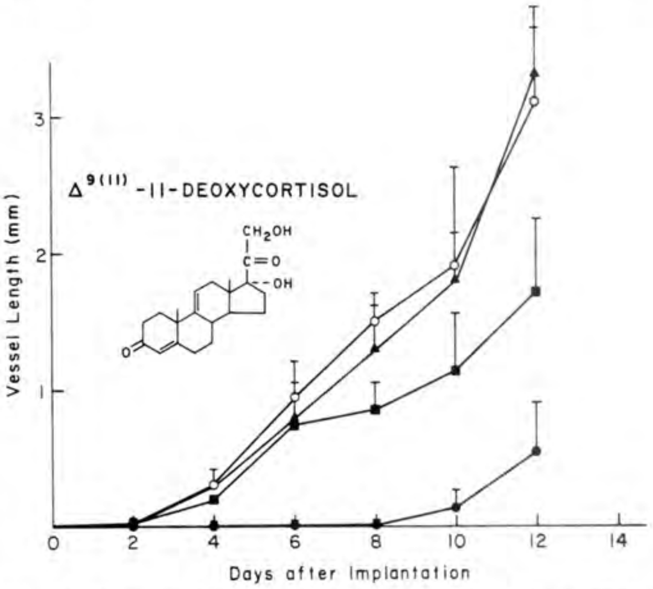


FIG. 5C. Mean growth rates (and SEM) of capillaries in Figure 5B. ● = $\Delta^{9(11)}$-11-deoxycortisol and heparin. ■ = $\Delta^{9(11)}$-11-deoxycortisol alone. ▲ = heparin alone. ○ = blank (empty polymer implant).

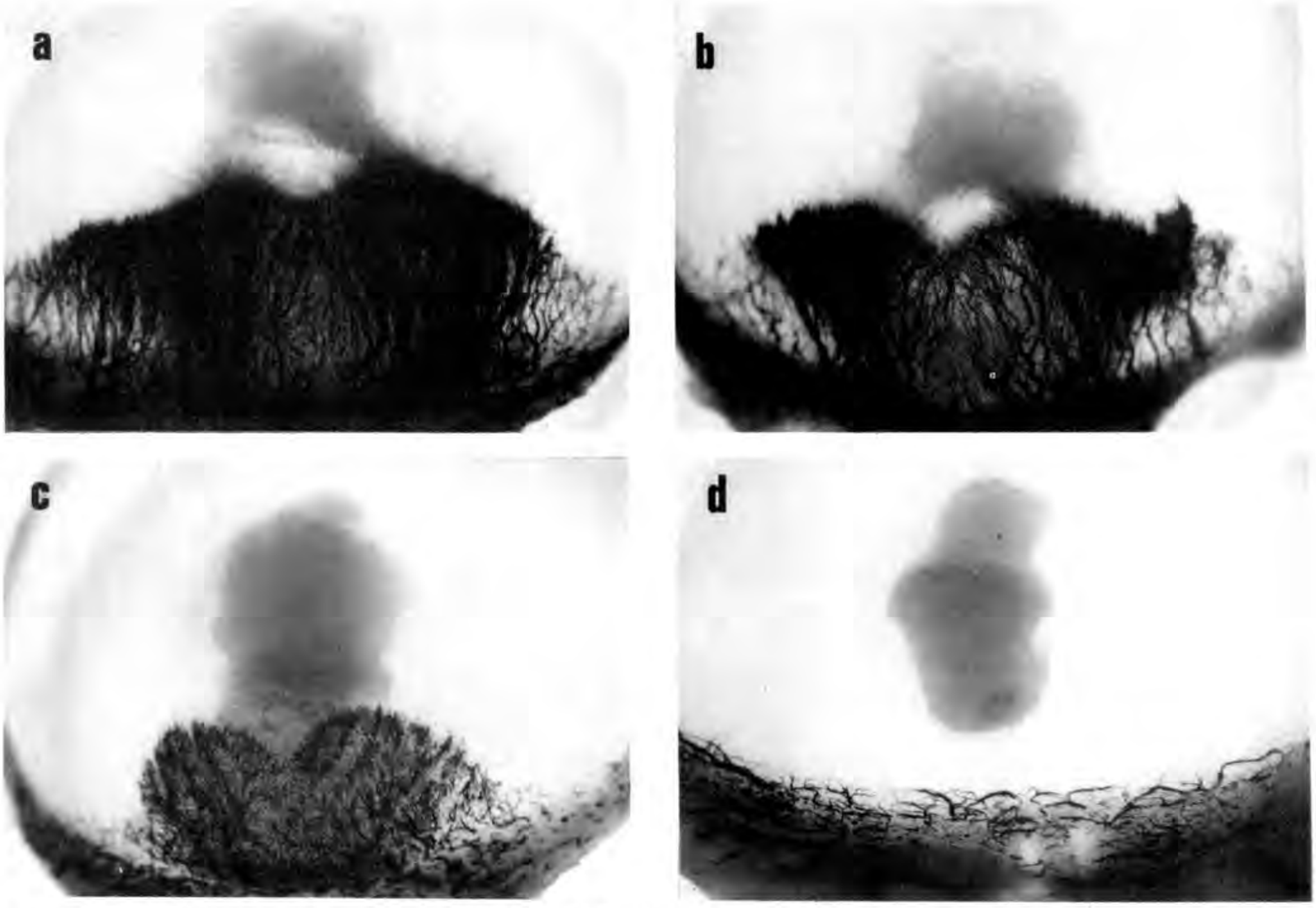
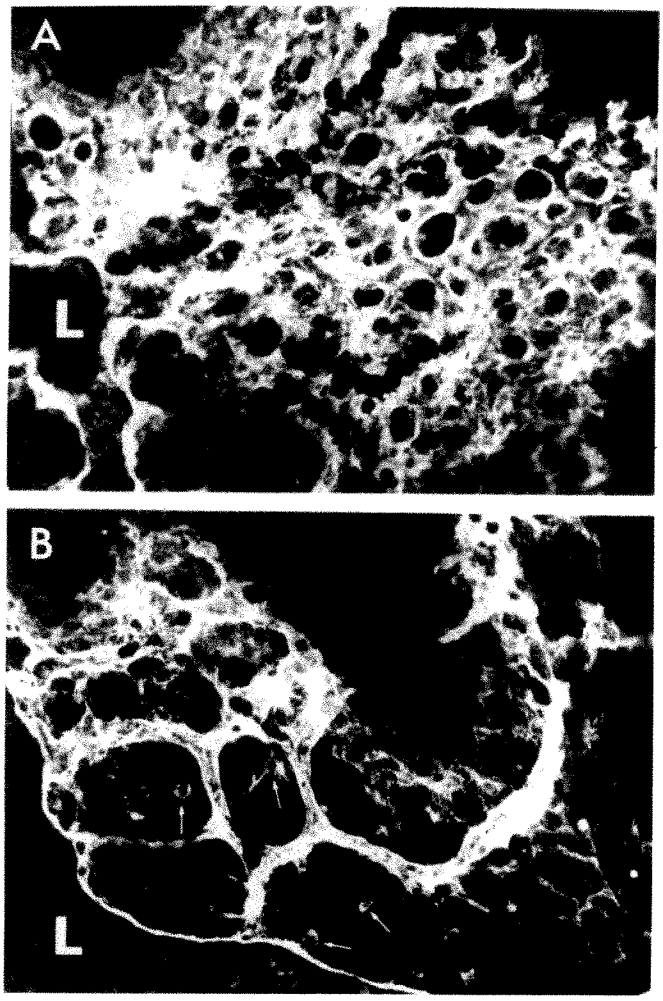


FIG. 5B. Rabbit corneas 11 days after intracorneal implant of V2 carcinoma (top of each photograph). Rabbits were killed and India ink was injected into both carotid arteries. A 1-mm^3 sustained-release pellet of ethylene vinyl acetate copolymer was implanted between the tumor and the vascular bed. It can be seen only in (*d*), and is obscured by a dense pannus of new capillaries in the other photographs. The polymer pellets contain heparin (Sigma), 1.8 μg/mL, and $\Delta^{9(11)}$-11-deoxycortisol, 135 μg/mL. (*a*) Blank (*i.e.*, empty polymer pellet). (*b*) Heparin alone. (*c*) Steroid alone. (*d*) Steroid-plus heparin. There is no vessel growth in (*d*) as long as the polymer pellet is present. When it is removed (up to 30 days after implant), new capillaries begin rapid growth.



FIGS. 6A and B. Fluorescence localization of fibronectin within *en face* paraffin sections of normal (*A*) and angiostatic steroid-treated (*B*) CAMs. *A*. In the normal subectodermal vascular bed, fibronectin appears in a continuous linear pattern delineating basement membrane that surrounds large vessels as well as capillary structures. Note the small intercapillary distances within the normal capillary plexus. The amorphous pattern of staining along the top of this view is due to fibronectin present within the overlying ectoderm basement membrane. *B*. In regions of partial capillary regression, the finest capillaries and associated linear patterns of fibronectin are lost first. Progression of capillary involution is associated with additional loss of fibronectin, capillary retraction, and endothelial cell rounding. Small arrows indicate rounded endothelial cells in contact with wisps of fibronectin-containing material; L = lumen of large vessel (×400). Affinity-purified rabbit antibodies to fibronectin were obtained courtesy of Joseph Madri (Yale) and used as previously described.[17]

the pathways by which heparin and heparin-like molecules are normally degraded.[32] Recent experiments done with Neil Chen[33] in our laboratory demonstrate that the administration of hydrocortisone with a sulfatase inhibitor[34] but *without* exogenous heparin is just as effective in causing capillary regression in the chick embryo as is the steroid with heparin. The steroid alone has no effect. We found that sulfatase activity is abundant in the chorioallantoic membrane. The added sulfatase inhibitor appears to retard degradation of heparin and allows endogenous heparin to accumulate locally. Thus, it is possible that endogenous heparin together with circulating angiostatic steroids may act at low concentrations over long periods to defend against abnormal capillary growth at the wrong place or time.

Mechanism of Action of Angiostatic Steroids

When the angiostatic steroids were first revealed, the only known model of regression of growing capillaries was our previous study of the morphologic events that followed the removal of an angiogenic stimulus from a neovascularized cornea.[35] In this experiment, removal of an angiogenic stimulus (ethylene vinyl acetate copolymer pellet containing tumor extract) led to platelet aggregation and the formation of microthrombi at the tips of the new capillaries within 24–48 hours. Endothelial cells desquamated and macrophages migrated into the lumen of the vessels to phagocytize platelets and dying endothelial cells. In contrast, when capillaries regressed under the influence of angiostatic steroids and heparin, histologic sections showed no platelet accumulation, macrophage infiltration, or microthrombi. This suggested that a novel mechanism of capillary involution was taking place.

A clue to such a mechanism came from an examination of what is known about other tissues that undergo physiologic involution, *e.g.*, the mammary gland[36] and the Mullerian duct.[37] Involution of epithelium in these tissues is associated with degradation of basement membrane. Furthermore, the modulation of basement membrane integrity in these epithelial tissues appears to be regulated through a balance of steroids and specific polypeptide growth factors.[38] By analogy, it seemed possible that angiostatic steroids could regulate the growth and viability of capillary endothelium through their effects on the capillary basement membrane. Degradation of basement membrane could lead to gradual rounding and eventual detachment of endothelial cells, as predicted by experimental models of epithelial cells.[39] Normal endothelial cells progressively lose their ability to grow as they take on increasingly rounded forms, even when supplied with optimal growth factors.[40] They die after only a few hours of detachment from a substratum.[41] The normal vascular basement membrane contains collagen type IV, laminin, fibronectin, and glycosaminoglycans. We used immunofluorescence microscopy to study the distribution of two basement membrane components, fibronectin and laminin (method described in Fig. 6 legend).

Dissolution of Vascular Basement Membrane Accompanies Involution of Growing Capillary Blood Vessels

Chorioallantoic membranes treated with steroid–heparin mixtures revealed avascular zones with complete loss of capillary structure in the center, and partial involution of capillary blood vessels at the periphery. At the periphery of the avascular zones, the distance between capillaries was more than 10-fold greater than normal intercapillary distance in untreated parts of the chorioallantoic membrane (Fig. 6). As the avascular zones developed over 48 hours, there was fragmentation of capillary basement membrane and progressive loss of fibronectin and laminin within the regions of capillary involution. Eventually these basement membrane components disappeared completely as the capillary itself underwent total involution. The rapid breakdown of capillary basement membrane in the steroid–heparin-treated embryos correlated with endothelial cell rounding and desquamation. Capillary retraction presented a pattern that was the reverse of capillary growth. In the treated embryos, the basement membranes of surrounding large vessels, nongrowing capillaries, and neighboring epithelium were not affected.

In contrast, in untreated embryos, or in those treated with heparin or steroid alone, fibronectin and laminin appeared in continuous linear patterns within the basement membrane surrounding growing capillaries. Fibronectin outlined both the large vessels and fine capillaries throughout the entire vascular network of the chorioallantoic membrane.

The pathway by which only basement membrane associated with growing capillaries breaks down, leaving basement membrane of neighboring epithelium and large vessels intact, is not obvious. Nevertheless, the specificity of angiostatic steroids for growing capillaries is unparalleled. A possible explanation for this specificity is that normal capillary growth may require high turnover rates of basement membrane. Adjacent tissue and larger vessels may have much slower basement membrane turnover. Basement membranes of large vessels are more heavily stained with fibronectin antibodies than are fine capillaries. Older capillaries that are not growing are surrounded by a slightly more dense basement membrane that contains increased amounts of laminin and type IV collagen.

This biological system has also made it possible to demonstrate that the relation between matrix dissolution and tissue involution clearly correlates with changes in cell shape. For example, endothelial cell rounding was generally associated with progressive degradation of the vascular basement membrane. This supports a concept that we previously proposed,[39,41] that cell shape and especially matrix-dependent alterations of cell shape, may serve as physiologic regulators of tissue development *in vivo.* In support of this hypothesis, we have recently been able to select successful pharmacologic inhibitors of angiogenesis based simply on their ability to modulate capillary endothelial cell form *in vitro.*

Further Evidence that Alterations in Extracellular Matrix Turnover are Involved in the Mechanism of Capillary Regression

Additional evidence of a causal role for extracellular matrix alterations in capillary regression was obtained by a study of drugs that interfere with deposition or processing of collagen, a major component of basement membrane. L-proline is an essential amino acid for the synthesis of collagen. Analogues of proline that can be incorporated in the place of proline have been shown to interfere with triple helix formation and to inhibit collagen deposition. Co-administration of these inhibitors of collagen production were found to markedly synergize the capacity of angiostatic steroids to cause capillary regression, even in the absence of heparin. The synergism was further potentiated when heparin was added.

L-azetidine carboxylic acid (LACA) is an analogue of proline that was the most active potentiator of angiostatic steroids. When administered with an angiostatic steroid and heparin, LACA gave more than a twofold increase in antiangiogenic activity in the chick embryo (95% avascular zones *vs.* 40% with steroid plus heparin without LACA). Furthermore, combinations of LACA with steroid were more antiangiogenic (73% avascular zones) than our original heparin–steroid combination (43% avascular zones). Thus, LACA was a stronger potentiator of angiostatic steroids than heparin. It is well known that analogues of proline can inhibit collagen deposition in a wide variety of growing tissues when given at high doses over prolonged periods. However, when administered at lower doses for shorter times in conjunction with angiostatic steroids, proline analogues appear to potentiate capillary regression in a specific fashion. This observation suggests the possibility of the future use of "combined modalities" in the treatment of angiogenesis-dependent diseases. These results also strongly support the concept that the alterations in extracellular matrix turnover that we previously observed play a central physiologic role in capillary regression.

Summary

A new class of angiostatic steriods has been identified. These steroids inhibit angiogenesis in the presence of a nonanticoagulant heparin fragment. Tetrahydrocortisol, a metabolite of cortisone previously believed to be biologically inactive, is now known to be one of the most potent of the naturally occurring steroids. Both its plasma and urinary forms are antiangiogenic. This finding was made because of our original misinterpretation that dexamethasone lacked antiangiogenic activity.

Induction of capillary basement membrane dissolution is the first biochemical action described for this new class of steroids. Angiostatic steroids appear to induce specific alterations in basement membrane turnover only within growing capillaries when administered with heparin or a heparin fragment. Chemical inhibitors of collagen deposition can have specific effects on capillary growth when co-administered with angiostatic steroids. These results suggest that distinct conformations of the steroid molecule convey specificity for growing capillary endothelial cells. Endogenous tissue heparin, when properly protected from degradation, similarly appears to be capable of synergizing with angiostatic steroids to specifically induce capillary regression. The identification of molecules with antiangiogenic activity suggests the potential existence of other naturally occurring inhibitors of capillary endothelial cell growth that may act physiologically to maintain the normal quiescent state of vascular endothelial cells.

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DISCUSSION

DR. FRANCIS MOORE (Boston, Massachusetts): As President Drake said yesterday, surgical work and surgical missions in our society change over time. One has been of importance for many years and is of growing importance today. That is the contributions of surgery to basic biomedical science.

This scientific contribution is not something that increases our income or fills our hospital beds, but it adds to the stature of surgery. It adds to our academic clout. It adds to the ability of all of us to obtain funds for our laboratories, and it lets society know that we are a scientific profession.

Dr. Judah Folkman's contributions are outstanding in this regard. There are now several hundred laboratories over the world working on angiogenesis, a word that Dr. Folkman coined and popularized many years ago when he first postulated the existence of angiogenic hormones, if you want to call them that.

Four chemical angiogenic structures have been identified currently. Two of them have been gene cloned. Thus, from a surgeon in our midst, has come a whole new field of science. I believe it is very exciting that our profession can continue to render this contribution to society as a whole and to Dr. Folkman we are grateful for his leadership.

I have two questions: first, many years ago, almost 33 years ago, we presented before this society a paper in which Dick Steenberg and Norman Gold were the chief authors, showing that THE and THF (tetrahydrocortisol and tetrahydro compound F) were very prominent in the urinary excretion of all surgical patients immediately after operation.

We were trying to outline the quantitative clinical and chemical kinetics of the adrenal response to surgery. Norman Gold discovered that these tetrahydro compounds were being excreted in the urine in large amounts after every surgical operation. We believed they were just totally inactive excretory-pathway steroids as the entire world believed until Dr. Folkman's paper this morning.

Therefore, it is interesting that after trauma there is a lag phase in wound healing. I ask Dr. Folkman if this burst of THE and THF that follows trauma acts by inhibiting the growth of new blood vessels. It might be responsible for the so-called lag phase of wound healing. Possibly that lag phase is important. When the wound has a pool of serum in it can it develop local concentrations of antibodies that are significant? Then, after a few days when the THE and the THF subside, the vessels can grow in and complete the job under the angiogenic influences.

My second question is the question that is on everyone's mind, and that is, has Dr. Folkman had an opportunity to experiment with THE and THF in tumors in the laboratory?

DR. JOSEPH E. MURRAY (Wellesley Hills, Massachusetts): Often when a person develops a highly visible profile in one phase of his professional life, there is a tendency to minimize his other talents. Everybody acknowledges Dr. Folkman's outstanding leadership in biological surgical research, but only those of us working daily with him realize his solid clinical judgments and skills and the extraordinary effect his inquisitive mind brings to the daily rounds of all of us working in the clinical services of the Children's Hospital.

Whether or not his studies lead ultimately to the control of neoplasms or to the control of arteriovenous malformations, his influence on the thinking and teaching of the staff, residents, and medical students is enormous. He is a superb, caring, clinical surgeon doing excellent research, and I believe that it is only appropriate for me to share these thoughts with all of the members of this Association.

DR. JUDAH FOLKMAN (Closing discussion): I want to thank Dr. Murray for his kind remarks. They were unsolicited. I especially want to thank Dr. Moore. I tell my house staff, "When you give your first paper at a national meeting, if you really want to understand what you have just said, ask Dr. Moore to open the discussion."

Dr. Moore's questions were important, and we really do not know yet what is going on physiologically with these metabolites. Here we have a picture of the endocrine system using breakdown products of cortisone to regulate the growth of the vascular system.

In answer to Dr. Moore's second question, we know much more about the pharmacologic effects of angiostatic steroids. It is possible in certain tumor-bearing mice, if you have the right heparin products, to regress some tumors, but large steroid doses are required.

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Book Reviews

William P. Longmire, Jr., M.D.
Advisor for Editorial Board
Los Angeles, California

H. Kim Lyerly, M.D.
Advisor for Residents in Surgery
Durham, North Carolina

Occlusive Cerebrovascular Disease: Diagnosis and Surgical Management. Thoralf M. Sundt, Jr. 506 pp. Philadelphia: W. B. Saunders Co. 1987. $85.00.

THIS EXCELLENT MONOGRAPH is an in-depth study based on the experience at Mayo Clinic, supplemented by extensive references from the literature. There are 37 contributors and 38 chapters. Dr Sundt, Chairman of Neurosurgery at Mayo, is author or co-author of 26 chapters. The text is divided into six sections, illustrating the comprehensive coverage: basic considerations, carotid artery surgery, reconstructive surgery for the aortic arch branches and the vertebral arteries, extracranial to intracranial bypass arterial pedicles, extracranial to intracranial bypass vein grafts, and intracranial small vessel surgery. There are also chapters on extracranial carotid aneurysms and carotid body tumors.

The author's classification of patients differs from that used by most surgeons, who divide patients into categories of stroke, transient ischemia, and asymptomatic stenosis. Sundt places patients into five groups depending on combined medical, neurological, and angiographically defined risk factors. While his is an excellent system, it does cause difficulty in comparing results with other series.

The author's technique of carotid endarterectomy includes general anesthesia, routine EEG monitoring with cerebral blood flow determination, selective shunting, and arteriotomy closure with vein patch graft reinforced with a Teflon wrap. The monitoring studies have produced unique data, a major contribution by Dr. Sundt and colleagues.

The sections on EC-IC bypass are based on a large experience. Caution is advised regarding indications for performing this operation.

The book is profusely illustrated with arteriograms, CT scans, and operative photographs. The anatomic and operative procedure drawings are superb.

There is one chapter on controversies in carotid surgery. Interestingly, there is only a brief discussion of surgery for asymptomatic lesions, a highly controversial matter, except for comments relative to asymptomatic stenosis contralateral to a previously symptomatic lesion treated by carotid endarterectomy.

This splended book is well written, informative, authoritative, and scholarly. It will be a useful reference for general vascular surgeons and especially neurosurgeons managing cerebrovascular disease.

JESSE E. THOMPSON, M.D.
Dallas, Texas

Atlas of General Surgery, 2nd Edition. Hugh Dudley, David C. Carter, R. C. G. Russell. 980 pp. Boston: Butterworths. 1986. $65.00.

THIS ATLAS has been skillfully culled from the massive multivolume work on operative surgery by Rob and Smith, which is now in its third edition. The result is 97 presentations with few words but many drawings of actual operations by medical artists of repute. Herein lies the book's strength and also its weakness.

The contributing surgeons are leading exponents in their own fields, preponderately British, but many from North America and a few from Australasia. Their advice, tersely presented, could hardly be bettered, but among them they have relied on the work of no less than 38 artists. While some produce clear helpful line drawings, such as those of Robert Lane who teams up with John Goligher, others have expressed what they saw with subtle shading, possibly originally in color, which does not lend itself so well for conveying the niceties of surgical technique.

The choice of incisions and their proper closure is a valuable addition as is the inclusion of special techniques such as the stapling gun for anastomoses in inaccessible sites. Cardiopulmonary surgery is particularly well covered with the various approaches to the thoracic cavity and operations on lungs, heart, and esophagus and bypass technology. Blood vessel techniques, which lend themselves particularly to illustration, are contributed by such well-known protagonists as Eastcott and Adams, but the endocrine surgeon is not so well served, parathyroid surgery is contributed by a urologist, and there is no mention of transplantation or storage of the glands.

The quality of reproduction of both the illustrations and the text is of the highest order and the proofreading meticulous. It is noticeable that many of the references are not recent, but this is something inherent in a book with so many contributors.

In brief this is an excellent guide to current surgical techniques and full of sound common sense in its advice to those in training. It would be a useful addition to the reference library of any theatre suite.

SELWYN TAYLOR
Sussex, England

Silvergirl's Surgery: The Veins. Harold Laufman. 273 pp. Austin: Silvergirl, Inc. 1986. $39.95.

HAROLD LAUFMAN, M.D., Ph.D., himself a scholar and authority on venous disease, has collected in one volume the articles he believes are the basic developments in our knowledge of the venous system of the extremities. In the opening section on surgical anatomy, he goes back to the drawings of Fabricius and William Harvey. Advancing to diagnostic tests for venous disease of the lower extremities, his selection includes the lectures of Brodie, McPheeters, Berberisch, and Hirsch, and dos Santos' first paper on phlebography in humans. In the section on treatment of varicose veins, he traces sclerotherapy from the original injection of iodine to the use of sodium morrhuate in 1930, citing the work of Tavel, Schiassi, Sicard, Linser, and Higgins. Under surgical treatment, he begins with the work of Benjamin Brodie on treatment of varicose veins of the leg and includes contributions by Trendelenburg, Perthes, Moore, Thomas, C.H. Mayo, Babcock, Colt, and Ochsner and Mahorner. Compression therapy for venous ulcer was developed by Unna, Gay, and in our generation, Linton.

He has collected also the outstanding original articles on the disease of thromboembolism, starting with Hunter, Davis, Paget, Lee, Mueller, Trendelenburg, Ochsner and DeBakey, Homans, and ending with Lazar Greenfield's report on transvenous removal of pulmonary emboli by vacuum-cup catheter technique. The section on ischemic thrombotic disease includes the work of Trousseau, Homans, Gregoire, Audier and Haimovici, Laewen, Leriche, and Ochsner and DeBakey.

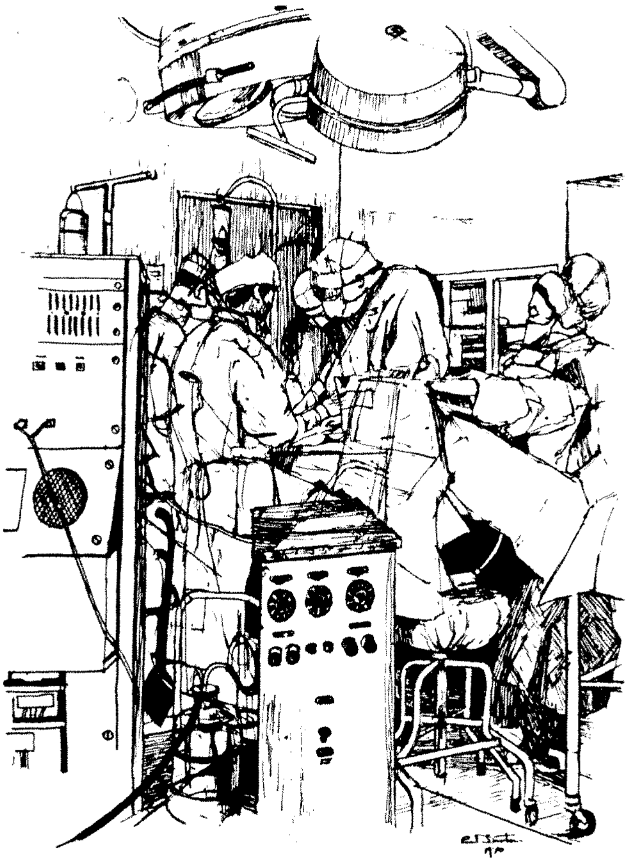
In the final section on the pharmacologic therapy of venous disease, his selection includes the work of Crafoord on postoperative treatment with heparin for the prevention of thrombosis, articles by Allen, Barker and Waugh, and Yin and Wessler on a naturally occurring plasma inhibitor of activated Factor X, plus contributions by Laufman himself, Jorpes, and, finally, by Robertson, Nilsson, and Nylander on the thrombolytic effect of streptokinase as evaluated by phlebography of deep venous thrombi of the leg.

Seldom has there appeared such a comprehensive collection of original work together with vintage woodcuts, historic phlebograms, excellent line drawings, and diagrams where needed. This volume is an archivist's treasure trove and deserves to be in medical libraries and on the shelf of physicians who study the history of vascular achievements as source material for new insight into contemporary research.

Had this volume been available when this reviewer was researching original, basic articles on venous disease, he could have spared himself much time and frustration. They are all here, complete with annotations. Another personal note: it was inspiring to find some of my teachers and colleagues included in this edition. Historic documents need not be dusty.

JOHN J. CRANLEY, JR., M.D.
Cincinnati, Ohio

SOUTHEAST ASIAN JOURNAL OF SURGERY



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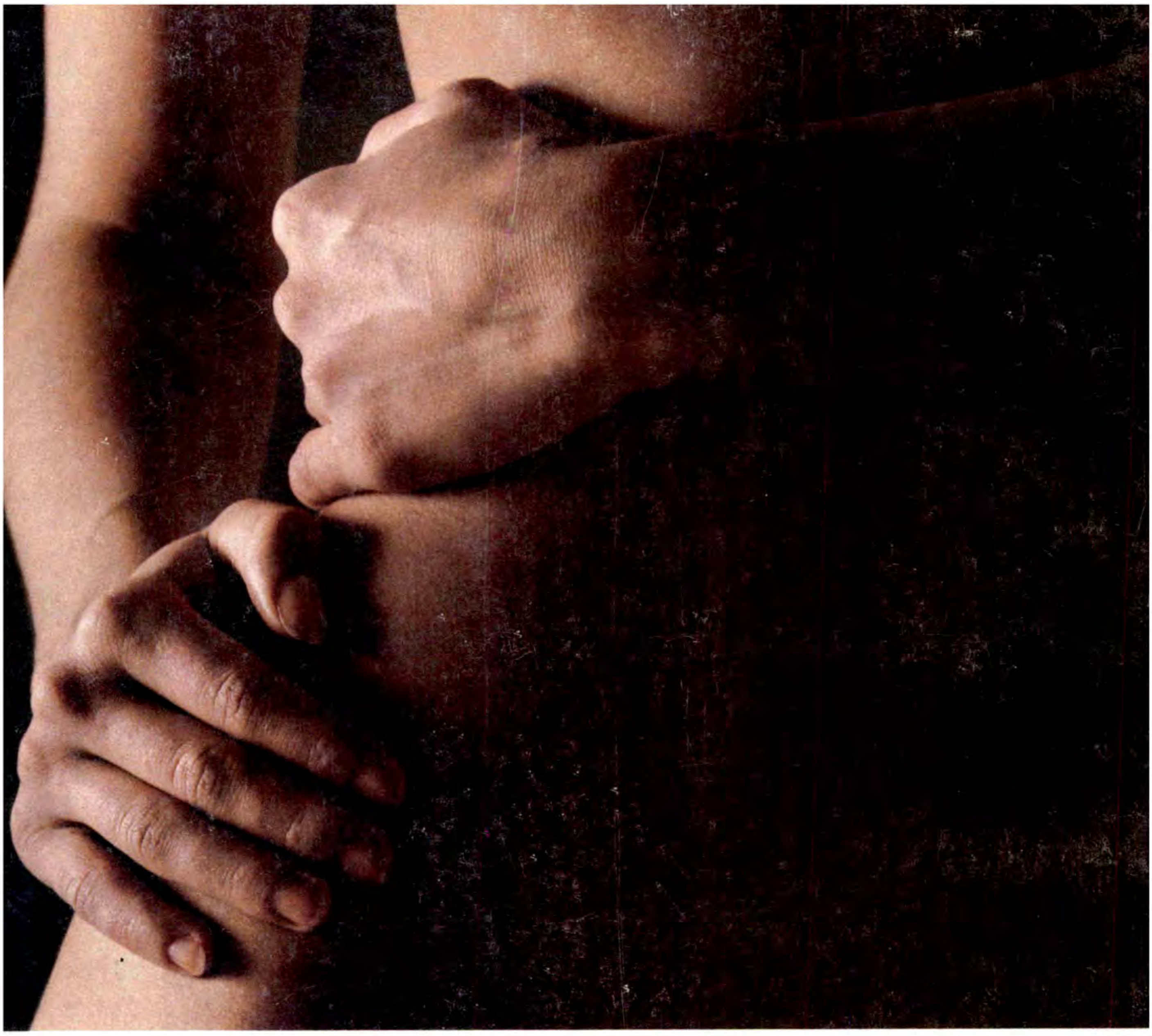

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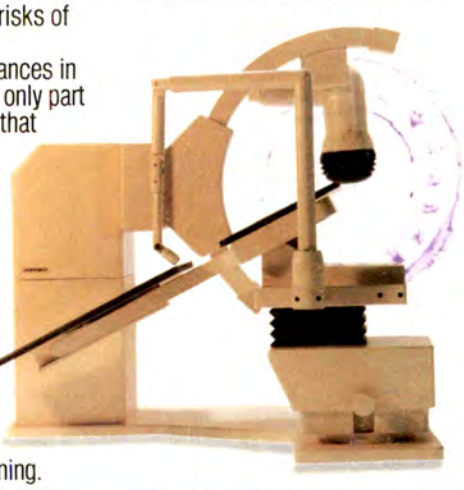

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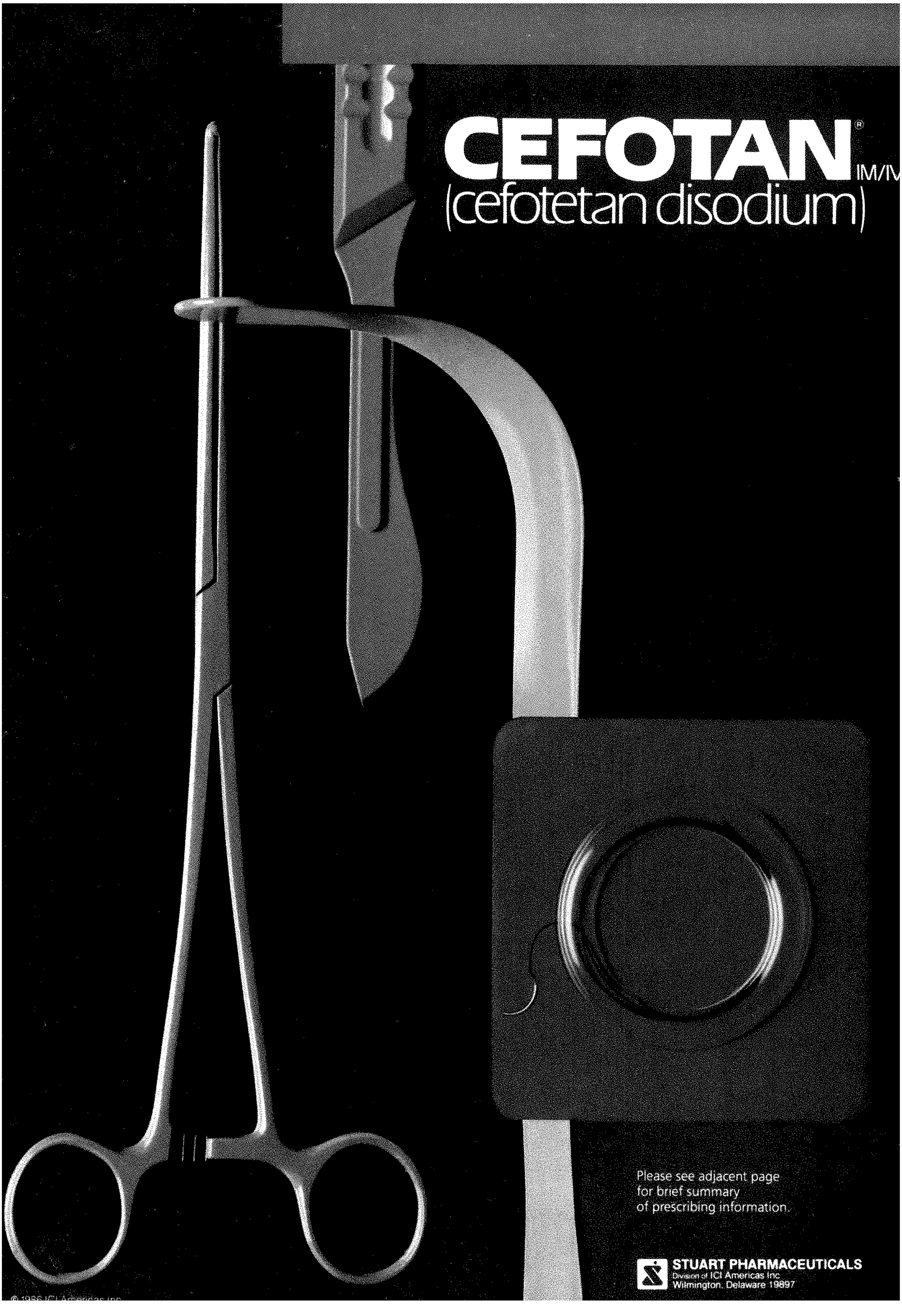

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INDICATIONS AND USAGE
TREATMENT: CEFOTAN® (cefotetan disodium) is indicated for the therapeutic treatment of the following infections when caused by susceptible strains of the designated organisms:

Urinary tract infections caused by *E coli*, *Klebsiella* species (including *K pneumoniae*), *Proteus mirabilis* and *Proteus* sp (which may include the organisms now called *Proteus vulgaris*, *Providencia rettgeri*, and *Morganella morganii*).

Lower respiratory tract infections caused by *Streptococcus pneumoniae* (formerly *D pneumoniae*), *Staphylococcus aureus* (penicillinase- and nonpenicillinase-producing strains), *Haemophilus influenzae* (including ampicillin-resistant strains), *Klebsiella* species (including *K pneumoniae*), and *E coli*.

Skin and skin structure infections caused by *Staphylococcus aureus* (penicillinase- and nonpenicillinase-producing strains), *Staphylococcus epidermidis*,* *Streptococcus pyogenes* and *Streptococcus* species (excluding enterococci), and *E coli*.

Gynecologic infections caused by *Staphylococcus aureus*† (including penicillinase- and nonpenicillinase-producing strains), *Staphylococcus epidermidis*,* *Streptococcus* species (excluding enterococci), *E coli*, *Proteus mirabilis*, *Neisseria gonorrhoeae*, *Bacteroides* species (excluding *B distasonis*, *B ovatus*, *B thetaiotaomicron*), *Fusobacterium* species,† and gram-positive anaerobic cocci (including *Peptococcus* and *Peptostreptococcus* species†).

Intra-abdominal infections caused by *E coli*, *Klebsiella* species (including *K pneumoniae*†), *Streptococcus* species (excluding enterococci), and *Bacteroides* species (excluding *B distasonis*, *B ovatus*, *B thetaiotaomicron*).

Bone and joint infections caused by *Staphylococcus aureus*.†

***NOTE:** Some strains of *Staphylococcus epidermidis* are resistant to cefotetan.

†Efficacy for this organism in this organ system was studied in fewer than ten infections.

PROPHYLAXIS: The preoperative administration of CEFOTAN may reduce the incidence of certain postoperative infections in patients undergoing surgical procedures that are classified as clean contaminated or potentially contaminated (eg, cesarean section, abdominal or vaginal hysterectomy, transurethral surgery, biliary tract surgery, and gastrointestinal surgery).

The prophylactic dose of CEFOTAN should be administered 30 to 60 minutes prior to surgery. In patients undergoing cesarean section, CEFOTAN should be administered intravenously after the clamping of the umbilical cord.

If there are signs and symptoms of infection, specimens for culture should be obtained for identification of the causative organism so that appropriate therapeutic measures may be initiated.

CONTRAINDICATIONS
CEFOTAN is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

WARNINGS
Before therapy with CEFOTAN is instituted, careful inquiry should be made to determine whether the patient has had previous hypersensitivity reactions to cefotetan disodium, cephalosporins, penicillins, or other drugs. This product should be given cautiously to penicillin-sensitive patients. Antibiotics should be administered with caution to any patient who has demonstrated some form of allergy, particularly to drugs. If an allergic reaction to CEFOTAN occurs, discontinue the drug. Serious acute hypersensitivity reactions may require epinephrine and other emergency measures.

Pseudomembranous colitis has been reported with the use of cephalosporins (and other broad-spectrum antibiotics); therefore, it is important to consider its diagnosis in patients who develop diarrhea in association with antibiotic use.

Treatment with broad-spectrum antibiotics may alter normal flora of the colon and may permit overgrowth of clostridia. Studies indicate a toxin produced by *Clostridium difficile* is one primary cause of antibiotic-associated colitis. Cholestyramine and colestipol resins have been shown to bind the toxin in vitro.

Mild cases of colitis may respond to drug discontinuance alone. Moderate to severe cases should be managed with fluid, electrolyte, and protein supplementation as indicated. When the colitis is not relieved by drug discontinuance, or when it is severe, oral vancomycin is the treatment of choice for antibiotic-associated pseudomembranous colitis produced by *C difficile*. Other causes should also be considered.

PRECAUTIONS
GENERAL: As with other broad-spectrum antibiotics, prolonged use of CEFOTAN may result in overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection does occur during therapy, appropriate measures should be taken.

In common with many other broad-spectrum antibiotics, CEFOTAN may be associated with a fall in prothrombin activity. Those at risk include patients with renal or hepatic impairment, or poor nutritional state. Prothrombin times should be monitored in patients at risk and exogenous Vitamin K administered as indicated.

CEFOTAN should be used with caution in individuals with a history of gastrointestinal disease, particularly colitis.

INFORMATION FOR PATIENTS: As with some other cephalosporins, a disulfiram-like reaction characterized by flushing, sweating, headache, and tachycardia may occur when alcohol (beer, wine, etc) is ingested within 72 hours after CEFOTAN administration. Patients should be cautioned about the ingestion of alcoholic beverages following the administration of CEFOTAN.

DRUG INTERACTIONS: If CEFOTAN and an aminoglycoside are used concomitantly, renal function should be carefully monitored, especially if higher dosages of the aminoglycoside are to be administered or if therapy is prolonged, because of the potential nephrotoxicity and ototoxicity of aminoglycoside antibiotics. Although, to date, nephrotoxicity has not been noted when CEFOTAN was given alone, it is possible that nephrotoxicity may be potentiated if CEFOTAN is used concomitantly with an aminoglycoside.

DRUG/LABORATORY TEST INTERACTIONS: A false positive reaction for glucose in urine may occur with Benedict's or Fehling's solution.

As with other cephalosporins, high concentrations of cefotetan may interfere with measurement of serum and urine creatinine levels of Jaffe reaction and produce false increases in the levels of creatinine reported.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY: Although long-term studies in animals have not been performed to evaluate carcinogenic potential, no mutagenic potential of cefotetan was found in standard laboratory tests.

Cefotetan has adverse effects on the testes of prepubertal rats. Subcutaneous administration of 500 mg/kg/day (approx 8-16 times the usual adult human dose) on days 6-35 of life (thought to be developmentally analogous to late childhood and prepuberty in humans) resulted in reduced testicular weight and seminiferous tubule degeneration in 10 of 10 animals. Affected cells included spermatogonia and spermatocytes; Sertoli and Leydig cells were unaffected. Incidence and severity of lesions were dose-dependent; at 120 mg/kg/day (approx 2-4 times the usual human dose), only 1 of 10 treated animals was affected, and the degree of degeneration was mild. Similar lesions have been observed in experiments of comparable design with other methylthiotetrazole-containing antibiotics and impaired fertility has been reported, particularly at high dose levels. No testicular effects were observed in 7-week-old rats treated with up to 1000 mg/kg/day SC for 5 weeks, or in infant dogs (3 weeks old) that received up to 300 mg/kg/day IV for 5 weeks. The relevance of these findings to humans is unknown.

USAGE IN PREGNANCY: Pregnancy Category B: Reproduction studies have been performed in rats and monkeys at doses up to 20 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to cefotetan. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

USAGE IN NURSING MOTHERS: Cefotetan is excreted in human milk in very low concentrations. Caution should be exercised when cefotetan is administered to a nursing woman.

PEDIATRIC USE: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS
In clinical studies the following adverse effects were considered related to CEFOTAN therapy.

Gastrointestinal symptoms occurred in 1.5 percent of patients; the most frequent were diarrhea (1 in 80) and nausea (1 in 700).

Hematologic laboratory abnormalities occurred in 1.4 percent of patients and included eosinophilia (1 in 200), positive direct Coombs' test (1 in 250), and thrombocytosis (1 in 300).

Hepatic enzyme elevations occurred in 1.2 percent of patients and included a rise in SGPT (1 in 150), SGOT (1 in 300), alkaline phosphatase (1 in 700), and LDH (1 in 700).

Hypersensitivity reactions were reported in 1.2 percent of patients and included rash (1 in 150) and itching (1 in 700).

Local effects were reported in less than one percent of patients and included phlebitis at the site of injection (1 in 300), and discomfort (1 in 500).

DOSAGE AND ADMINISTRATION
TREATMENT: The usual adult dosage is 1 or 2 grams of CEFOTAN administered intravenously or intramuscularly every 12 hours for 5 to 10 days. Proper dosage and route of administration should be determined by the condition of the patient, severity of the infection, and susceptibility of the causative organism.

GENERAL GUIDELINES FOR DOSAGE OF CEFOTAN

Type of Infection	Daily Dose	Frequency and Route
Urinary Tract	1-4 grams	500 mg every 12 hours IV or IM 1 or 2 g every 24 hours IV or IM 1 or 2 g every 12 hours IV or IM
Other Sites	2-4 grams	1 or 2 g every 12 hours IV or IM
Severe	4 grams	2 g every 12 hours IV
Life-Threatening	6* grams	3 g every 12 hours IV

*Maximum daily dosage should not exceed 6 grams.

PROPHYLAXIS: To prevent postoperative infection in clean contaminated or potentially contaminated surgery in adults, the recommended dosage is 1 or 2 g of CEFOTAN administered once, intravenously, 30 to 60 minutes prior to surgery. In patients undergoing cesarean section, the dose should be administered as soon as the umbilical cord is clamped.

IMPAIRED RENAL FUNCTION: When renal function is impaired, a reduced dosage schedule must be employed. The following dosage guidelines may be used.

DOSAGE GUIDELINES FOR PATIENTS WITH IMPAIRED RENAL FUNCTION

Creatinine Clearance mL/min	Dose	Frequency
>30	Usual Recommended Dose*	Every 12 hours
10-30	Usual Recommended Dose*	Every 24 hours
<10	Usual Recommended Dose*	Every 48 hours

*Dose determined by the type and severity of infection, and susceptibility of the causative organism.

Cefotetan is dialyzable and it is recommended that for patients undergoing intermittent hemodialysis, one-quarter of the usual recommended dose be given every 24 hours on days between dialysis and one-half the usual recommended dose on the day of dialysis.

HOW SUPPLIED
CEFOTAN is a dry, white to pale yellow powder supplied in vials containing cefotetan disodium equivalent to 1 g and 2 g cefotetan activity for intravenous and intramuscular administration. The 1 g dose is available in 10 mL and 100 mL vials, and the 2 g dose is available in 20 mL and 100 mL vials. The vials should not be stored at temperatures above 22°C and should be protected from light.

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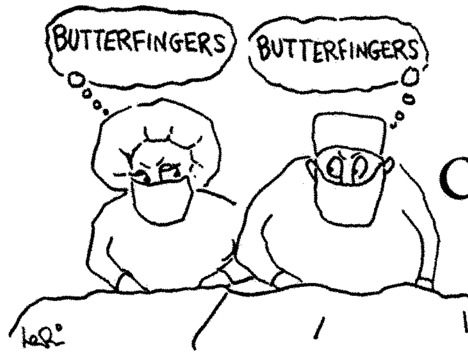

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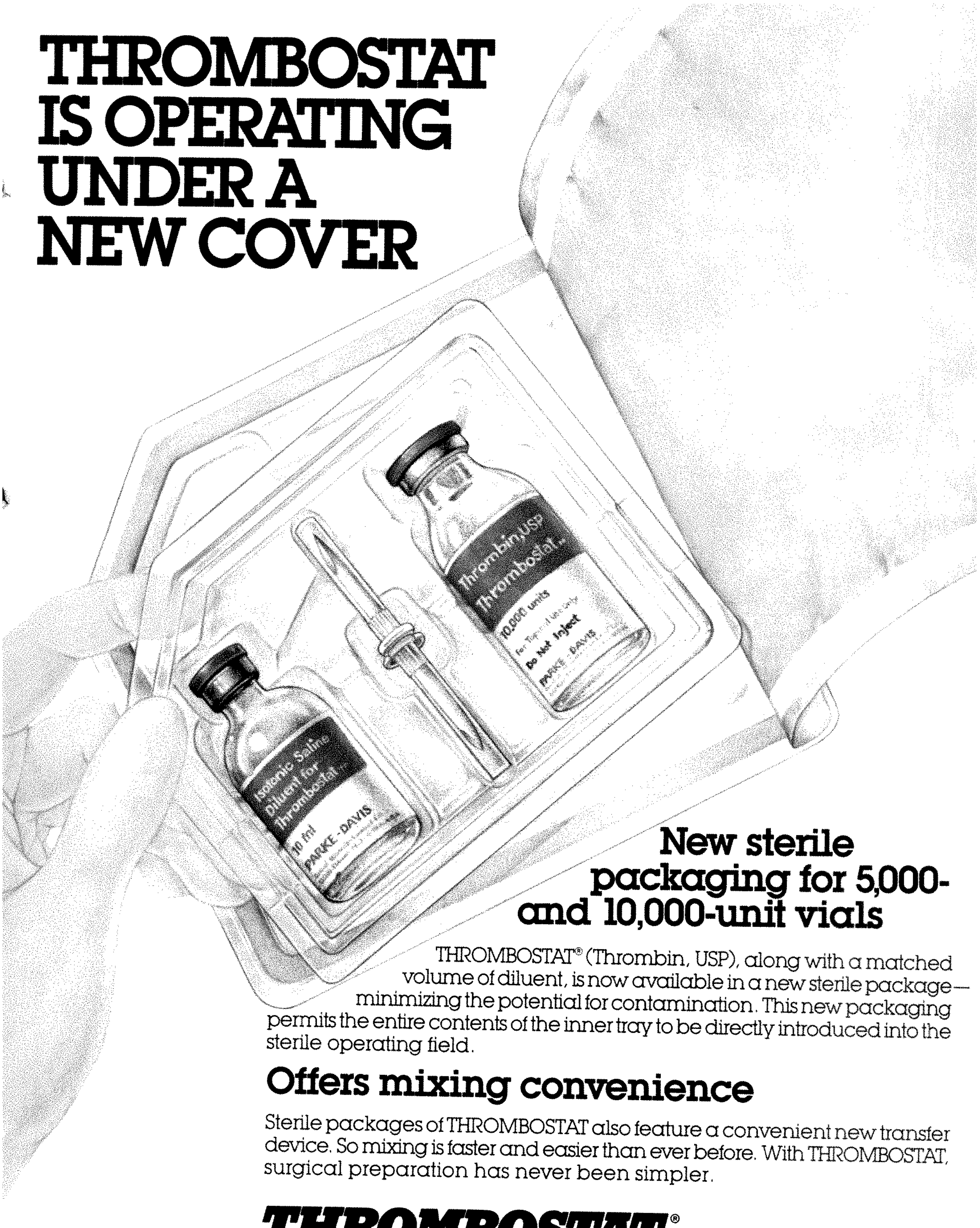

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THROMBOSTAT® THROMBIN, USP
(Bovine Origin)

Before prescribing, please see full prescribing information. A Brief Summary follows:

Thrombostat must not be injected! Apply on the surface of bleeding tissue as a solution or powder.

INDICATIONS AND USAGE
Thrombostat (Thrombin, USP) is indicated as an aid in hemostasis wherever oozing blood from capillaries and small venules is accessible.

In various types of surgery, solutions of Thrombostat may be used in conjunction with Absorbable Gelatin Sponge, USP for hemostasis.

CONTRAINDICATIONS
Thrombostat is contraindicated in persons known to be sensitive to any of its components and/or to material of bovine origin.

WARNING
Because of its action in the clotting mechanism, Thrombostat must not be injected or otherwise allowed to enter large blood vessels. Extensive intravascular clotting and even death may result. Thrombostat is an antigenic substance and has caused sensitivity and allergic reactions when injected into animals.

PRECAUTIONS
General:
Consult the absorbable gelatin sponge product labeling for complete information for use prior to utilizing the thrombin-saturated sponge procedure.

Pregnancy—
Teratogenic effects: Pregnancy Category C. Animal reproduction studies have not been conducted with Thrombin, Topical (Bovine). It is also not known whether Thrombin, Topical (Bovine) can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Thrombin, Topical (Bovine) should be given to a pregnant woman only if clearly indicated.

Pediatric Use:
Safety and effectiveness in children have not been established.

ADVERSE REACTIONS
Allergic reactions may be encountered in persons known to be sensitive to bovine materials.

DOSAGE AND ADMINISTRATION
General: Solutions of Thrombostat may be prepared in sterile distilled water or isotonic saline. The intended use determines the strength of the solution to prepare. For general use in plastic surgery, dental extractions, skin grafting, neurosurgery, etc., solutions containing approximately 100 units per mL are frequently used. For this, 10 mL of diluent added to the 1000 unit package is suitable. Where bleeding is profuse, as from cut surfaces of liver and spleen, concentrations as high as 1000 to 2000 units per mL may be required. For this the 5000 unit vial dissolved in 5 mL or 2.5 mL, respectively, of the diluent supplied in the package is convenient. Intermediate strengths to suit the needs of the case may be prepared by selecting the proper strength package and dissolving the contents in an appropriate voulme of diluent. In many situations, it may be advantageous to use Thrombostat in dry form on oozing surfaces.

Caution: Solutions should be used immediately upon reconstitution. If necessary, refrigerate the solution and use within 3 hours of reconstitution.

The following techniques are suggested for the topical application of Thrombostat.

1. The recipient surface should be sponged (not wiped) free of blood before Thrombostat is applied.
2. A spray may be used or the surface may be flooded using a sterile syringe and small gauge needle. The most effective hemostasis results when the Thrombostat mixes freely with the blood as soon as it reaches the surface.
3. In instances where Thrombostat in dry form is needed, the vial is opened by removing the metal ring by flipping up the plastic cap and tearing counterclockwise. The rubber-diaphragm cap may be easily removed and the dried Thrombostat is then broken up into a powder by means of a sterile glass rod or other suitable sterile instrument.
4. Sponging of treated surfaces should be avoided in order that the clot remain securely in place.

Thrombostat may be used in conjunction with Absorbable Gelatin Sponge USP as follows:

1. Prepare Thrombostat solution of the desired strength.
2. Immerse sponge strips of the desired size in the Thrombostat solution. Knead the sponge strips vigorously with moistened gloved fingers to remove trapped air, thereby facilitating saturation of the sponge.
3. Apply saturated sponge to bleeding area. Hold in place for 10 to 15 seconds with a pledget of cotton or a small gauze sponge.

Sterile Packages
Thrombostat Sterile Packages are available in two strengths, 5000 units and 10,000 units. A Sterile Package contains one sterile vial of Thrombostat, one sterile vial of Isotonic Saline Diluent, and one sterile transfer device. The Sterile Package may be used as follows:

1. Remove the Tyvek® blister lid by pulling up at the indicated corner. The sterile inner tray can be lifted out or introduced into the operating field.
2. The cover to the sterile inner tray is removed by pulling up on the finger tab, exposing the sterile contents.
3. Thrombostat solution of the desired strength is prepared using the transfer device.
4. Alternatively, when Thrombostat in dry form is needed, the vial is opened as described above and the dried Thrombostat broken up into a powder by means of a sterile glass rod or other suitable sterile instrument.

Thrombostat Kit
Thrombostat Kit contains one sterile 20,000 unit vial of Thrombostat, one sterile vial of Isotonic Saline Diluent, and one sterile pump sprayer cap. The kit may be used as follows:

1. Remove the Tyvek® blister lid by pulling up at the indicated corner. The sterile inner tray can be lifted out or introduced into the operating field.
2. The cover to the sterile inner tray is removed by pulling up on the finger tab, exposing the sterile contents.
3. Thrombostat solution of the desired strength is prepared and the pump sprayer cap inserted and seated on the Thrombostat solution vial. Note: Several strokes of the pump sprayer will be required before the Thrombostat solution is expelled.
4. Alternatively, when Thrombostat in dry form is needed, the vial is opened as described above and the dried Thrombostat broken up into a powder by means of a sterile glass rod or other suitable sterile instrument.

Caution—Federal law prohibits dispensing without prescription.

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No therapy

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Adjuvant Monotherapy

Now, the treatment of choice

A recent National Institutes of Health consensus report states that following surgery, "Tamoxifen [NOLVADEX] should now be regarded as standard therapy for postmenopausal patients with positive axillary lymph nodes and positive hormone receptor status."[1]

NOLVADEX increases disease-free time[2-5] by delaying recurrence following total mastectomy and axillary dissection in postmenopausal women with breast cancer (T_{1-3}, N_1, M_0). Moreover, NOLVADEX improves overall survival, with a 34% reduction in risk of mortality, as observed in the NOLVADEX Adjuvant Trial Organization (NATO) study.[4] This treatment is extremely well tolerated by patients[2-5]; in fact, one double-blind, placebo-controlled study demonstrated a NOLVADEX side effects profile similar to placebo.[2] And, since NOLVADEX has a mild side effects profile and is easy to administer, patients are afforded a better quality of life. NOLVADEX—today's promising breast cancer therapy for the postmenopausal woman—in the adjuvant setting and in metastatic disease.

Please see next page for brief summary of prescribing information.

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Nolvadex®

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BRIEF SUMMARY

INDICATIONS AND USAGE: NOLVADEX is effective in the treatment of metastatic breast cancer in postmenopausal women. Available evidence indicates that patients whose tumors are estrogen receptor positive are more likely to benefit from NOLVADEX therapy.

NOLVADEX is effective in delaying recurrence following total mastectomy and axillary dissection in postmenopausal women with breast cancer (T1-3, N1, M0). The estrogen and progesterone receptor values may help to predict whether NOLVADEX therapy is likely to be beneficial. In some NOLVADEX adjuvant studies, most of the benefit to date has been in the subgroup with 4 or more positive axillary nodes.

CONTRAINDICATIONS: None known.

WARNINGS: Pregnancy Category D: NOLVADEX may cause fetal harm when administered to a pregnant woman. Individuals should not become pregnant while taking NOLVADEX. Effects on reproductive functions are expected from the antiestrogenic properties of the drug. In reproductive studies in rats at dose levels equal to or below the human dose, nonteratogenic developmental skeletal changes were seen and were found to be reversible. In addition, in fertility studies in rats and in teratology studies in rabbits using doses at or below those used in humans, a lower incidence of embryo implantation and a higher incidence of fetal death or retarded in utero growth were observed, with slower learning behavior in some rat pups. The impairment of learning behavior did not achieve statistical significance in one study, and, in another study where significance was reported, this was by comparing dosed animals with controls of another study. Several pregnant marmosets were dosed during organogenesis or in the last half of pregnancy. No deformations were seen and although the dose was high enough to terminate pregnancy in some animals, those that did maintain pregnancy showed no evidence of teratogenic malformations. There are no adequate and well-controlled studies in pregnant women. There have been reports of spontaneous abortions, birth defects, fetal deaths, and vaginal bleeding. If this drug is used during pregnancy or the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

Ocular changes have been reported in a few patients who, as part of a clinical trial, were treated for periods greater than one year with NOLVADEX at doses at least four times the highest recommended daily dose of 40 mg. The ocular changes consist of retinopathy and, in some patients, there are also corneal changes and a decrease in visual acuity.

In addition, a few cases of ocular changes including visual disturbance, corneal changes, and/or retinopathy have been reported in patients treated with NOLVADEX at recommended doses. It is uncertain if these effects are due to NOLVADEX.

As with other additive hormonal therapy (estrogens and androgens), hypercalcemia has been reported in some breast cancer patients with bone metastases within a few weeks of starting treatment with NOLVADEX. If hypercalcemia does occur, appropriate measures should be taken and, if severe, NOLVADEX should be discontinued.

PRECAUTIONS: General: NOLVADEX should be used cautiously in patients with existing leukopenia or thrombocytopenia. Observations of leukopenia and thrombocytopenia occasionally have been made, but it is uncertain if these effects are due to NOLVADEX therapy. Transient decreases in platelet counts, usually to 50,000-100,000/cu mm, infrequently lower, have been occasionally reported in patients taking NOLVADEX for breast cancer. No hemorrhagic tendency has been recorded and the platelet counts returned to normal levels even though treatment with NOLVADEX continued.

Laboratory Tests: Periodic complete blood counts, including platelet counts, may be appropriate.

Carcinogenesis: While no conventional bioassay has been conducted, endocrine changes in immature and mature mice were investigated in a 13-month study. Granulosa cell ovarian tumors and interstitial cell testicular tumors were found in mice receiving NOLVADEX, but not in the controls.

Mutagenesis: No genotoxic potential has been found in a battery of in vivo and in vitro tests with pro- and eukaryotic test systems with drug metabolizing systems present.

Impairment of Fertility: Fertility in female rats was decreased following administration of 0.04 mg/kg for 2 weeks prior to mating through day 7 of pregnancy. There was a decreased number of implantations, and all fetuses were found dead.

Following administration to rats of 0.16 mg/kg from days 7-17 of pregnancy, there were increased numbers of fetal deaths. Administration of 0.125 mg/kg to rabbits during days 6-18 of pregnancy resulted in abortion or premature delivery. Fetal deaths occurred at higher doses. There were no teratogenic changes in either rat or rabbit segment II studies. Several pregnant marmosets were dosed with 10 mg/kg/day either during organogenesis or in the last half of pregnancy. No deformations were seen, and, although the dose was high enough to terminate pregnancy in some animals, those that did maintain pregnancy showed no evidence of teratogenic malformations. Rats given 0.16 mg/kg from day 17 of pregnancy to 1 day before weaning demonstrated increased numbers of dead pups at parturition. It was reported that some rat pups showed slower learning behavior, but this did not achieve statistical significance in one study, and in another study where significance was reported, this was by comparing dosed animals with controls of another study.

The recommended daily human dose of 20-40 mg corresponds to 0.4-0.8 mg/kg for an average 50 kg woman.

Pregnancy Category D: See WARNINGS.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from NOLVADEX, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

ADVERSE REACTIONS: The most frequent adverse reactions to NOLVADEX are hot flashes, nausea and vomiting. These may occur in up to one-fourth of patients, but are rarely severe enough to require discontinuation of treatment.

Less frequently reported adverse reactions are vaginal bleeding, vaginal discharge, menstrual irregularities and skin rash. Usually these have not been of sufficient severity to require dosage reduction or discontinuation of treatment.

Increased bone and tumor pain and, also, local disease flare have occurred, which are sometimes associated with a good tumor response. Patients with increased bone pain may require additional analgesics. Patients with soft tissue disease may have sudden increases in the size of preexisting lesions, sometimes associated with marked erythema within and surrounding the lesions and/or the development of new lesions. When they occur, the bone pain or disease flare are seen shortly after starting NOLVADEX and generally subside rapidly.

Other adverse reactions which are seen infrequently are hypercalcemia, peripheral edema, distaste for food, pruritus vulvae, depression, dizziness, light-headedness and headache. There have been infrequent reports of thromboembolic events occurring during NOLVADEX therapy. Since for cancer patients in general an increased incidence of thromboembolic events is known to occur, a causal relationship to NOLVADEX remains conjectural. An increased incidence has been reported when cytotoxins are combined with NOLVADEX.

If adverse reactions are severe, it is sometimes possible to control them by a simple reduction of dosage without loss of control of the disease.

OVERDOSAGE: Acute overdosage in humans has not been reported. Signs observed at the highest doses following studies to determine LD_{50} in animals were respiratory difficulties and convulsions. No specific treatment for overdosage is known; treatment must be symptomatic.

DOSAGE AND ADMINISTRATION: One or two 10 mg tablets twice a day (morning and evening). In the three single agent adjuvant NOLVADEX studies noted above (See Clinical Pharmacology), NOLVADEX was administered for two years. The optimal duration of adjuvant therapy is not known.

HOW SUPPLIED: Tablets containing tamoxifen as the citrate in an amount equivalent to 10 mg of tamoxifen (round, biconvex, uncoated, white tablet identified with NOLVADEX 600 debossed on one side and a cameo debossed on the other side) are supplied in bottles of 60 tablets and 250 tablets. Protect from heat and light.

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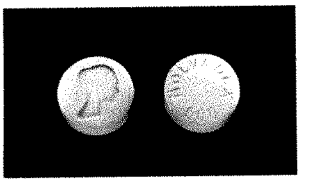

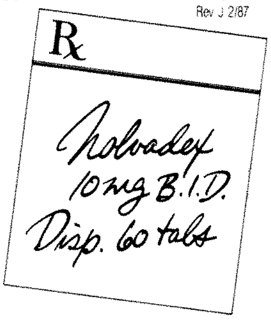

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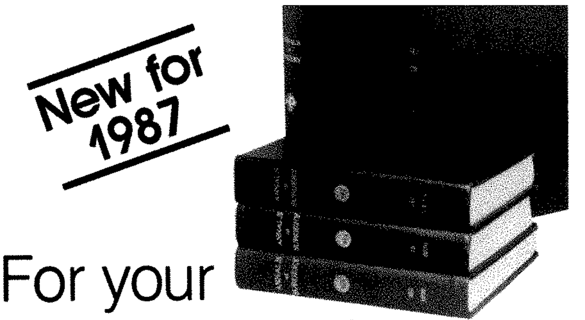

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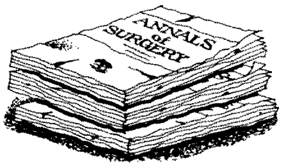

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ASE # 24 **AGE:** 55 **SEX:** FEMALE

IAGNOSIS: CECAL CARCINOMA

YMPTOMS: ANEMIA (Hg 6 gm/dl)

PERATION: RIGHT HEMICOLECTOMY & GASTROSTOMY

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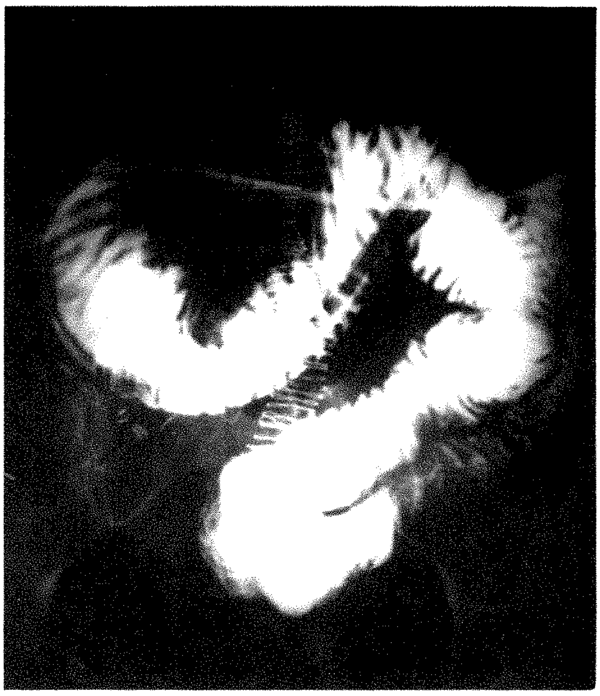
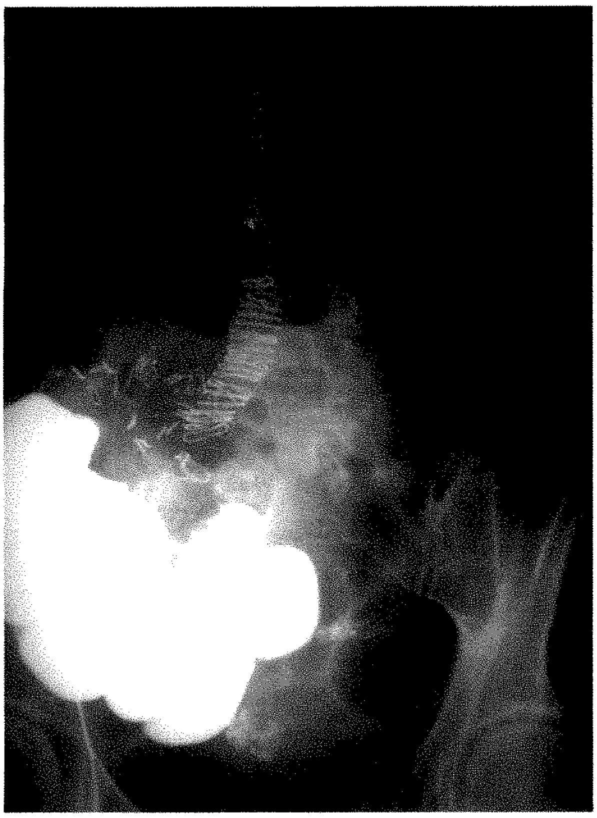
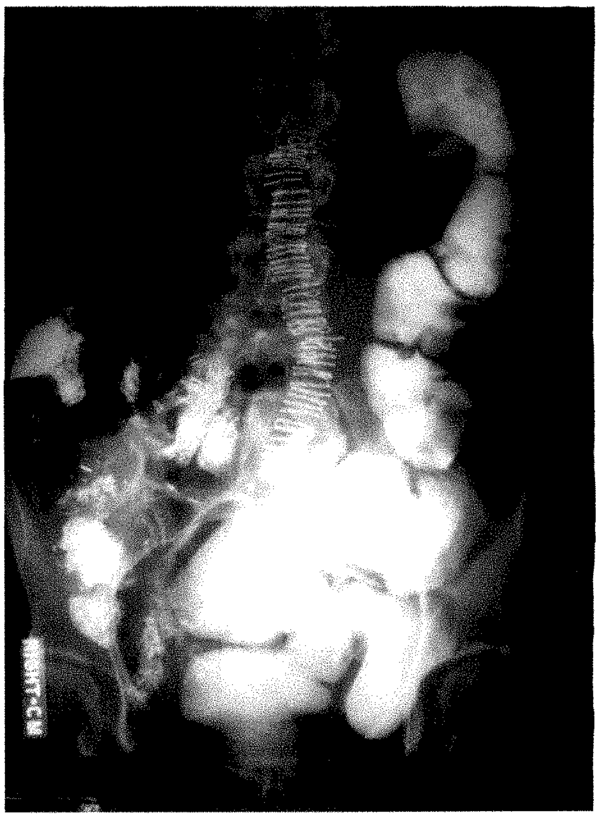
She received 300 ml/hr of Vivonex TEN (Norwich Eaton harm), absorbed 5,000 kcal the initial 20 hours, and then lerated a general diet. She was the 4th patient discharged neventfully 24 hours after bowel resection and reanastomosis.



A. Study @ 5 minutes (5 hours postop).
Note efficient removal of all excess barium, with none reaching the stomach.



B. Motility @ 4 hours (9 hours postop).
All barium is within the ileum.



C. Motility @ 16 hours (21 hours postop).
Barium is exiting in a spontaneous bowel movement.

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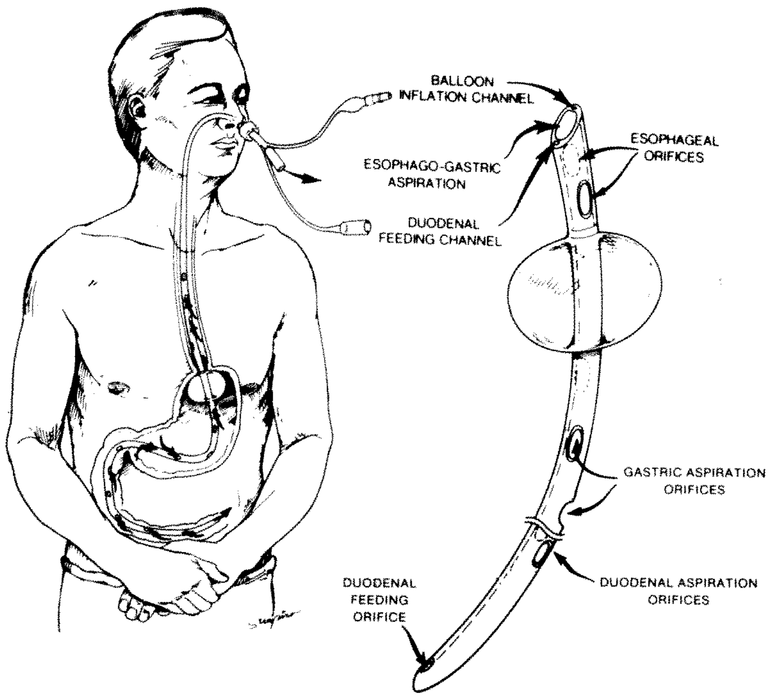
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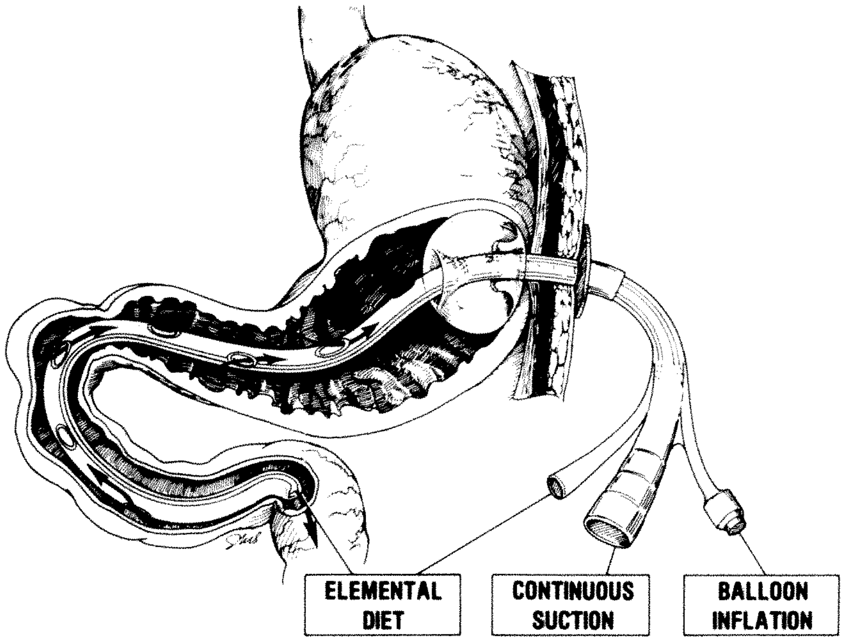

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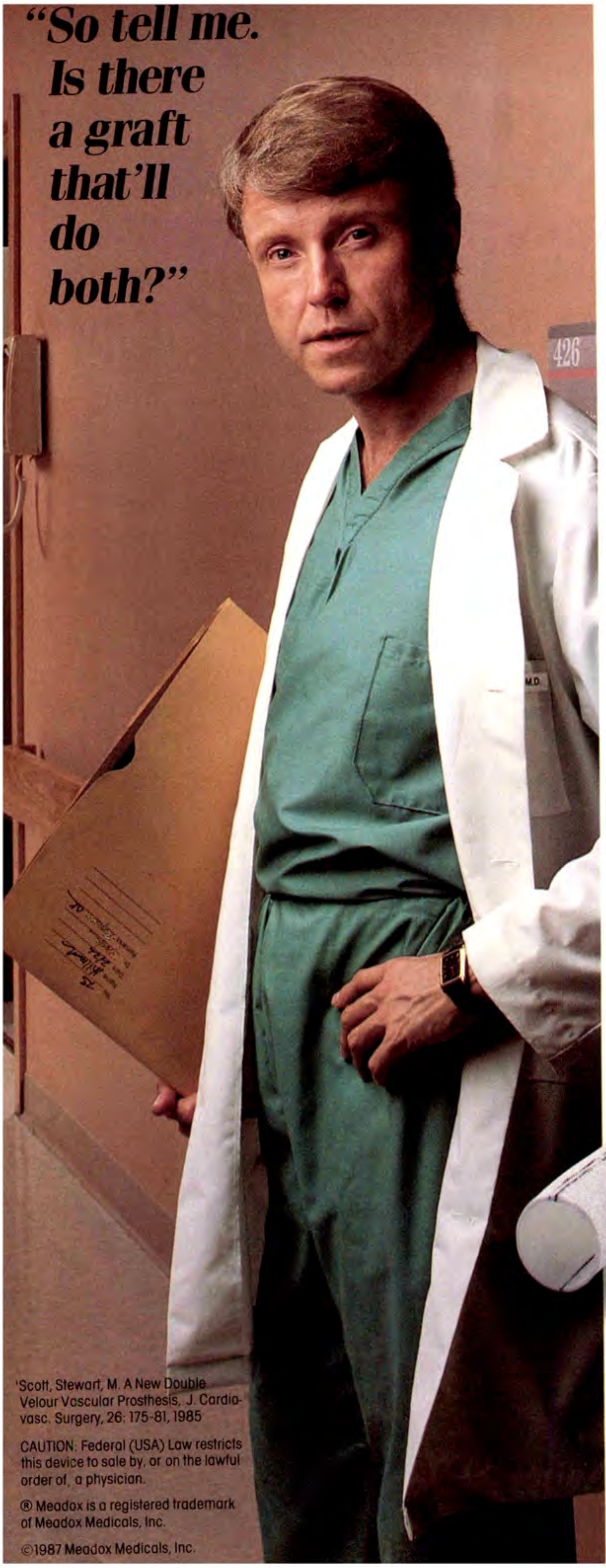

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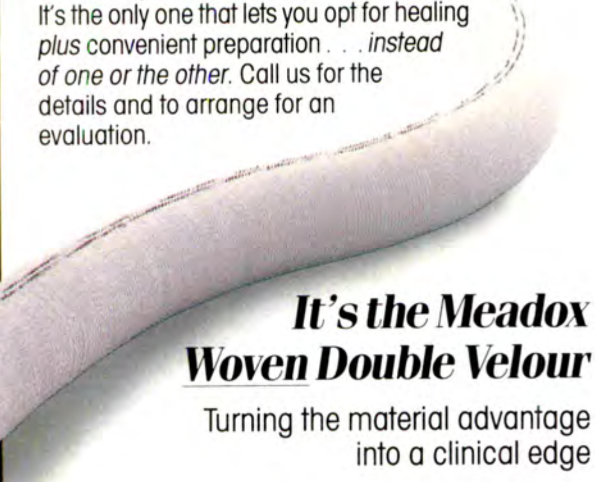

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[1] Scott, Stewart, M. A New Double Velour Vascular Prosthesis, J. Cardiovasc. Surgery, 26: 175-81, 1985

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The First 100 Liver Transplants at UCLA

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A clinical program in liver transplantation was begun at UCLA in 1984 after a period of laboratory investigation. The first 100 orthotopic liver transplants (OLT) were performed in 83 patients (43 adults and 40 children) between February 1, 1984 and November 1, 1986. Donors and recipients were matched only for size and ABO blood group compatibility, with OLT performed across blood groups in 28 patients. Standard operative techniques were used, including venous–venous bypass in adults. Arterial reconstruction was performed using an aortic Carrel patch or "branch patch" in 65% of cases and by end-to-end or aortic conduit techniques in the remainder. The hepatic artery thrombosis rate was 5%. Biliary reconstruction was choledochocholedochostomy in 67 OLT and Roux-en-Y choledochojejunostomy in 33 (complication rate of 24% and 24%, respectively). Average lengths and ranges of donor liver ischemia, operating time, and blood replacement were 4 hours (range: 1–10 hours), 7.6 hours (range: 4–15 hours), and 17 units packed cells (range: 2–220 units). Immunosuppressive regimen was cyclosporine–steroid combination, with monoclonal anti-T-cell antibody (OKT3) used for refractory rejection. All patients had one or more complications: pulmonary (78%), infectious (51%), renal dialysis (25%), neurologic (22%). All patients had at least one episode of acute rejection, and 3.6% had chronic rejection. Retransplantation was needed in nine patients once and in four patients twice. The overall retransplant survival rate was 54%, and two of four patients who received a second retransplant are alive. Sixty-three of the 83 patients (76%) are alive (adults 72%, children 80%). The 1- and 2-year actuarial survival rate is 73% (adults 68%, children 78%). Thirty-eight of 43 patients (88%) who had transplantation in the past year are alive. Of 14 perioperative variables assessed as predictors of early mortality, only postoperative dialysis ($p < 0.0005$) and presence of severe rejection ($p < 0.01$) had statistical significance. Seventy per cent of adults returned to work, and 84% of children had normal or accelerated growth. A new program in liver transplantation provides a dramatic option in patient care and an academic stimulus to the entire medical center.

Presented at the 107th Annual Meeting of the American Surgical Association, Palm Beach, Florida, April 21–23, 1987.

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TABLE 1. *Pediatric Patients Evaluated and Transplanted February 1, 1984–November 1, 1986*

Diseases	Patients Evaluated	Patients Transplanted*	Survival (%)
Biliary atresia			
Biliary atresia	40	18 (4)†	14/18 (78)
Biliary hypoplasia	1	1	1/1 (100)
Alagille's syndrome	1	0	—
Cirrhosis			
Idiopathic cholestasis/ cirrhosis	9	2	2/2 (100)
Familial cirrhosis	4	2 (1)	2/2 (100)
Chronic active hepatitis	2	1	1/1 (100)
Congenital hepatic fibrosis	1	0	—
Metabolic disorders			
Hemophilia	1	0	—
Alpha-1-antitrypsin deficiency	10	6	5/6 (83)
Wollmans syndrome	1	0	—
Tyrosinemia	2	2	0/2 (0)
San Fillipo syndrome	1	1 (1)	1/1 (100)
Wilson's disease	1	0	—
Inflammatory diseases			
Acute hepatic necrosis	5	2	1/2 (50)
Subacute hepatic necrosis	1	1	1/1 (100)
Reye's syndrome	1	0	—
Tumors			
Hepatoblastoma	4	1	1/1 (100)
Hemangioendothelioma	1	1	1/1 (100)
Metastatic Leiomyosarcoma	1	1	1/1 (100)
Miscellaneous			
Budd-Chiari syndrome	1	1 (1)	1/1 (100)
Total	88	40 (7)	32/40 (80)

* Retransplants in parentheses.
† One patient retransplanted twice.

THE FIRST HUMAN ORTHOTOPIC LIVER TRANSPLANT (OLT) was performed in 1963.[1] Although this achievement marked a dramatic surgical milestone, two decades would pass before clinical liver transplantation was recognized by a national medical consensus as a therapeutic option for patients with end-stage liver disease. During those 20 years, intensive laboratory and clinical investigation was conducted primarily by Starzl and colleagues[2,3] and later by Calne et al.[4] on immunology, technique, and applications of the procedure.

At the time of the National Institutes of Health Consensus Conference on Liver Transplantation in 1983,[5] there was only one major center in the United States (Denver/Pittsburgh) with a sizeable experience in OLT. Several other centers had reactivated or initiated new programs. By 1987, over 50 centers in the U.S. have programs in OLT, emphasizing the rapid acceptance of this therapy. At the University of California at Los Angeles (UCLA), a liver transplant program was organized in 1983, and the first clinical transplant was performed on February 1, 1984. Between that date and November 1, 1986, 100 transplants were performed in 83 patients. Forty-seven transplants that have been performed in 40 children (less than 18 years of age) and 53 transplants in 43 adults form the basis of this report.

Materials and Methods

The organization, development, and structure of the UCLA Program have been described.[6-8] The Liver Transplant Team includes the following individuals involved with the day-to-day care of both adults and children: surgeons (4), anesthesiologists (2), surgical residents (2), and a surgical fellow, anesthesia fellow, hepatologist, nephrologist, infectious disease specialist, psychiatrist, social worker, clinical nurse coordinator, donor nurse coordinator, administrative coordinator, and perfusionist. Personnel involved in the care of pediatric patients specifically include hepatologists (3) and specialists in critical care, nephrology, infectious diseases, and psychiatry. Prospective transplant recipients are evaluated in the hospital on the pediatric or adult liver transplant services and presented to the multidisciplinary Patient Selection Committee, which considers both adult and pediatric candidates. All patients are managed before and after operation by the surgical team in close collaboration with either the adult or pediatric specialists.

Patients Evaluated and Transplanted

Two hundred thirty-six patients were evaluated for transplantation. The diagnoses of these patients evaluated and transplanted and the individual survivals are shown in Tables 1 and 2. Mean age for children was 5 years with a range of five months to 16 years. Biliary atresia and its variants were the diseases seen and transplanted most frequently among children (Table 1). End-stage cirrhosis from various causes and metabolic disorders, particularly alpha-1-antitrypsin deficiency, were also common. Inflammatory diseases were seen less often, and only a few pediatric patients were evaluated for hepatic tumors. Mean age for adults was 41 years with a range of 18–60 years. Among adults, chronic active hepatitis, primary biliary cirrhosis, sclerosing cholangitis, and cryptogenic cirrhosis were the most common diseases seen and transplanted (Table 2).

Follow-up for all patients transplanted has been 100%. Range of follow-up is 1–33 months with a mean of 11.8 months. Each patient is numbered by transplant.

Donors and recipients were matched for size (weight and height) and ABO blood groups. No prospective tissue matching was performed. Transplants were performed across blood groups in 28 patients. In 24 of these patients, a Type O liver was placed in an A or B recipient. In four patients, a Type A or B liver was placed in an O recipient because of an urgent need for transplantation (two retransplants and two first transplants).

Twenty patients (12 pediatric and 8 adult) who had been accepted for transplantation died before a suitable donor could be found. Average age of the pediatric patients was 9.5 months (range 6–16 months). Diagnoses were biliary atresia in nine patients (previous portoenterostomy procedure in 7) and fulminant liver failure, Wilson's disease, and end-stage cholestatic cirrhosis in one patient each. All had severely depressed hepatic synthetic function. Adults who died while waiting for transplantation included three patients with chronic active hepatitis, two with cryptogenic cirrhosis, and one each with primary biliary cirrhosis, protoporphyria, and fulminant hepatic necrosis. Overall, for every three pediatric patients transplanted, one died waiting; for every five adults, one died waiting.

TABLE 2. *Adult Patients Evaluated and Transplanted, February 1, 1984–November 1, 1986*

Diseases	Patients Evaluated	Patients Transplanted*	Survival (%)
Inflammatory			
Acute/subacute hepatic necrosis	5	2 (1)	2/2 (100)
Sclerosing cholangitis	24	7 (2)†	5/7 (71)
Cirrhosis			
Chronic active hepatitis	45	12 (1)	9/12 (75)
Primary biliary cirrhosis	35	10	8/10 (80)
Cryptogenic cirrhosis	15	4 (3)†	3/4 (75)
Alcoholic cirrhosis	5	1	0/1 (0)
Metabolic			
Alpha-1-antitrypsin deficiency	2	1	1/1 (100)
Hemophilia	1	0	—
Protoporphyria	1	0	—
Tumors			
Hepatocellular carcinoma	4	2 (1)	1/2 (50)
Schwannoma	1	1	0/1 (0)
Hemangioendothelioma	1	1	1/1 (100)
Leiomyosarcoma (metastatic)	1	0	—
Embryonal sarcoma	1	0	—
Miscellaneous			
Budd-Chiari syndrome	5	2 (2)†	1/2 (50)
Polycystic kidney and liver disease	2	0	—
Total	148	43 (10)	31/43 (72)

* Retransplants in parentheses.
† One patient retransplanted twice.

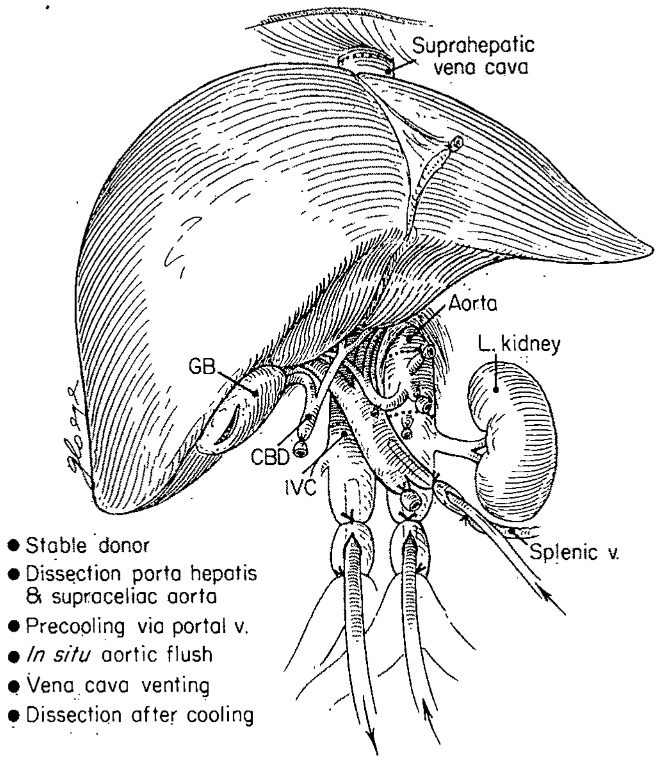

FIG. 1. Preparation for harvesting of the donor liver.

Operative Approach and Complications

Donor and recipient operations were performed using techniques described by Starzl et al.[9] Ninety-eight of 100 liver harvests were performed by members of our team who traveled to the donor hospital. In two cases, another team, Pittsburgh and Dallas, performed the donor hepatectomy and sent the organ to UCLA. The donor procedure allows for harvesting of heart, liver, and kidneys[10,11] (Fig. 1).

For the recipient, large-bore intravenous catheters and Silastic (Hickman® or Broviac®) catheters were placed before operation. Pulmonary artery monitoring, always used in adults, was rarely used in children except in teenagers. The abdomen was entered *via* a bilateral subcostal incision with midline extensions to the xiphoid in adults. A thoracotomy extension was used only once (OLT #64), and one patient (OLT #23) required transdiaphragmatic intrapericardial control of the inferior vena cava because of extensive previous surgery. No irreversible surgical maneuvers were performed during recipient hepatectomy before return of the donor liver to UCLA, although a satisfactory liver was harvested in every instance. In one case, recipient hepatectomy was not begun when the donor liver was found to be cirrhotic. Transplantation was also aborted in one patient with a hepatoblastoma and in one patient with hepatocellular carcinoma who were found to have tumor ex-

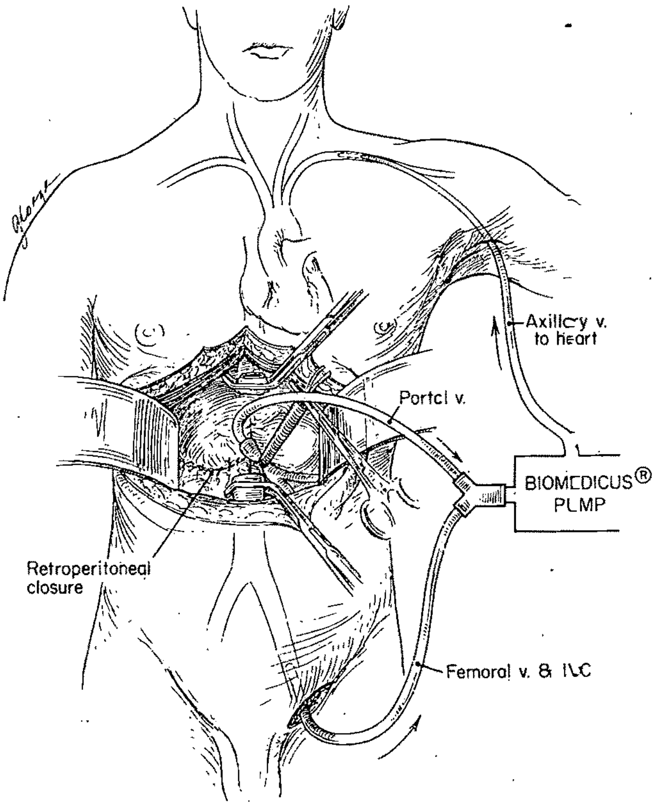

FIG. 2. Venous–venous bypass for circulatory support during the anhepatic phase.

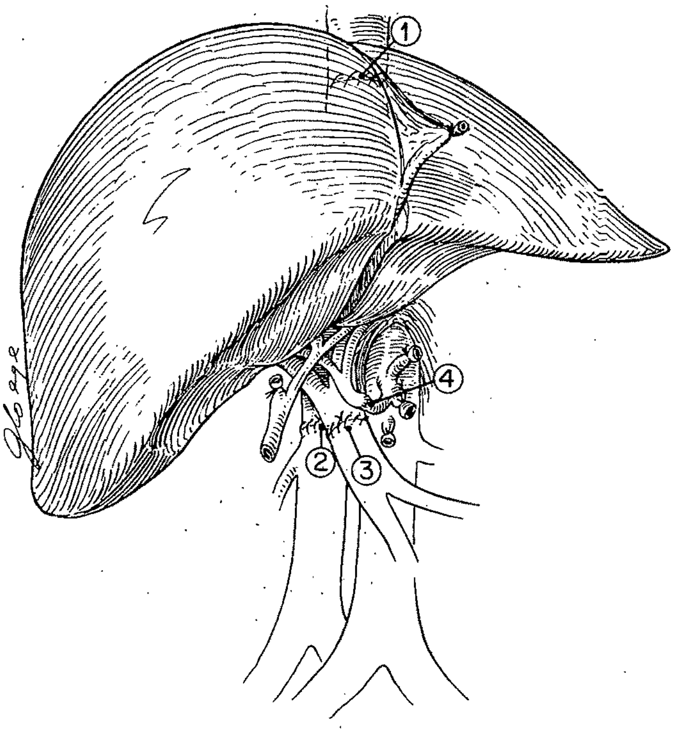

FIG. 3. Order of vascular anastomoses (see text).

tension beyond the liver thus precluding a curative resection.

Before removal of the native liver, trial clamping of the vena cava was performed. This was tolerated well in 44 of 100 transplants. Venous–venous bypass using femoral and portal venous return and axillary venous inflow, a routine in adults, was used in only three children, two (ages 14 and 15 years) who exhibited hypotension on trial clamping and one (OLT #23) with massive bleeding from multiple adhesions and portal hypertension who was placed on bypass for circulatory support (Fig. 2).

Vascular Anastomoses

Anastomoses were performed in the following order: suprahepatic inferior vena cava (IVC), infrahepatic IVC, portal vein, and hepatic artery (Fig. 3). While the infrahepatic IVC was being completed, the liver was flushed with cold normal saline solution *via* an indwelling portal vein cannula that had been placed for precooling during the donor hepatectomy. In the latter part of the series, 25 g of mannitol were added to the flushing solution. After the portal vein anastomosis was completed, the vena caval clamps were removed and the liver was reperfused with portal blood while the arterial anastomosis was performed.

Venous. The supra- and infrahepatic inferior vena caval and portal venous anastomoses were performed using a running polypropylene suture (3-0 or 4-0 for vena cava and 6-0 or 7-0 for portal vein). The posterior wall was sewn from within, with care taken to achieve an everting intima-to-intima approximation. An interrupted anterior row was used in small children to allow for growth of the vessel. "Growth factors" were used occasionally in adults.[12]

Arterial. Arterial reconstruction (Table 3) was variable and depended on donor and recipient anatomy.[13] Although most donor livers had normal (Type 1) arterial anatomy, variants were seen in 19 cases: 10 Type 2 (replaced left hepatic artery arising from left gastric artery), two Type 4 (right hepatic replaced from superior mesenteric and left hepatic replaced from left gastric arteries), and seven Type 3 (right hepatic replaced from superior mesenteric artery [SMA]). Recipient arterial anatomy was Type 2 in two cases, Type 3 in one case, and Type 1 in all others.

Running or interrupted sutures of 6-0 or 7-0 polypropylene were used for arterial anastomoses. A "branch patch" technique described by our group was often used to facilitate anastomosis of small vessels.[14]

An aortic Carrel patch of the entire donor celiac artery used in 21 transplants was sewn to a branch patch of the proper hepatic-gastroduodenal bifurcation (9 transplants), to a branch patch of the common hepatic bifurcation (7), to a branch patch of the celiac-splenic bifurcation (3), to the aorta (2), and to the common hepatic, and SMA (1 each). Although use of the celiac-hepatic trunk with a Carrel patch generally produced a redundant lie that would seem to be prone to kinking, no instances of arterial thrombosis occurred with this reconstruction.

A simple end-to-end technique was used in 21 transplants: hepatic-to-hepatic (13), hepatic-to-celiac (1), and celiac-to-hepatic (5), hepatic-to-recipient aorta with iliac graft (1), and donor SMA trunk-to-recipient celiac axis (1). There was one episode of thrombosis treated with retransplantation and arterial reconstruction using an aortic conduit (OLT #26).

A primary branch patch technique was used in 42 transplants. In 28 transplants, the hepatic artery or celiac-splenic bifurcation was sewn to a branch patch of the hepaticogastroduodenal bifurcation. In one transplant, the hepatic artery was sewn to a branch patch of the common hepatic bifurcation. In the donor with a double replaced arterial supply, the proximal SMA was joined to the celiac and the distal SMA to a branch patch of the hepaticogastroduodenal bifurcation. There were three thromboses, one of the celiac axis branch patch-to-recipient aorta and two of the hepatic-to-hepatic gastroduodenal branch patch type. One (OLT #27) thrombosis of the left hepatic artery occurred and produced left lobar necrosis and a biliary fistula. The lobar necrosis manifested as Citrobacter sepsis and was treated with operative lobar debridement; the later biliary fistula was treated with Roux-en-Y jejunal onlay on the fistulous orifice. The other thromboses (OLT #36 and OLT #79) involved the entire artery and were treated successfully with two subsequent retransplants in one patient and with a single retransplant in the other.

An aortic conduit from donor-to-recipient aorta was used in eight transplants, principally in our early experience. The initial episode of thrombosis in OLT #36 was managed with retransplantation and arterial reconstruction using an aortic conduit and an iliac artery interposition graft. This in turn thrombosed, and arterial anastomosis in the successful third transplant was performed using an aortic Carrel patch to a branch patch of the celiac-splenic bifurcation.

All thromboses occurred in the pediatric patients, and it is our impression that the majority occurred because of the small caliber of the donor arteries. Arterial inflow was tested carefully, and if it did not appear to be adequate, an alternative inflow was chosen. This experience with arterial reconstruction has indicated that each anastomosis must be individualized to accommodate the variable anatomy of donor and recipient.

TABLE 3. *Arterial Reconstruction*

	Donor Anatomy Type					
	N	1	2	3	4	Thrombosis
Aortic Carrel patch	19	13	4	2		
End-to-end	24	18	4	2		1
"Branch patch"	46	41	1	2	2	3*
Aortic conduit	8	7	1			1
End-to-side	3	2		1		
Total	100	81	10	7	2	5

* 1 left lobar infarction.

Biliary Reconstruction

The biliary anastomosis was a choledochocholedochostomy with a t-tube stent in 67 transplants and Roux-en-Y choledochojejunostomy with a straight tube or internal stent in 33 transplants (Fig. 4). Technetium-HIDA hepatobiliary scintigraphy was found useful for postoperative evaluation of the biliary anastomoses as well as of graft function.[15]

The overall biliary complication rate was 24%. There were 16 complications of choledochocholedochostomy (24%): bile peritonitis in nine after t-tube removal (reoperation required in 2), t-tube malposition or migration in four (reoperation in 2), biliary fistula in two, and bile duct tumor recurrence in one (anastomotic and distant recurrence). There were eight complications of choledochojejunostomy (24%). Five complications were related to duct-jejunal anastomosis: fistulas in three (one due to hepatic artery thrombosis), obstruction in one, and a tube problem in one. Three complications were related to the jejunojejunal anastomosis: perforation in two and bleeding in one. There were no deaths attributable to biliary complications, although one patient died of recurrent cholangiocarcinoma.

Other Operative Considerations

Average length of liver ischemia was 4 hours (range: 1–10 hours); of operation, 7.6 hours (range: 4–15 hours); and of anesthesia, 8.4 hours (range: 5.5–16 hours). Average requirements for blood and products were: packed red cells, 17.0 units (range: 2–220 units); fresh frozen plasma, 18.2 units (range: 2–190 units); platelets, 14.7 units (range: 0–100 units). Re-exploration for bleeding was necessary in 17 of 100 transplants; only two of these were done in the past year.

Splenectomy was performed in five patients, one at the time of the transplant to permit abdominal closure (OLT #33) and four later. One late splenectomy was done for thrombocytopenia from hypersplenism (OLT

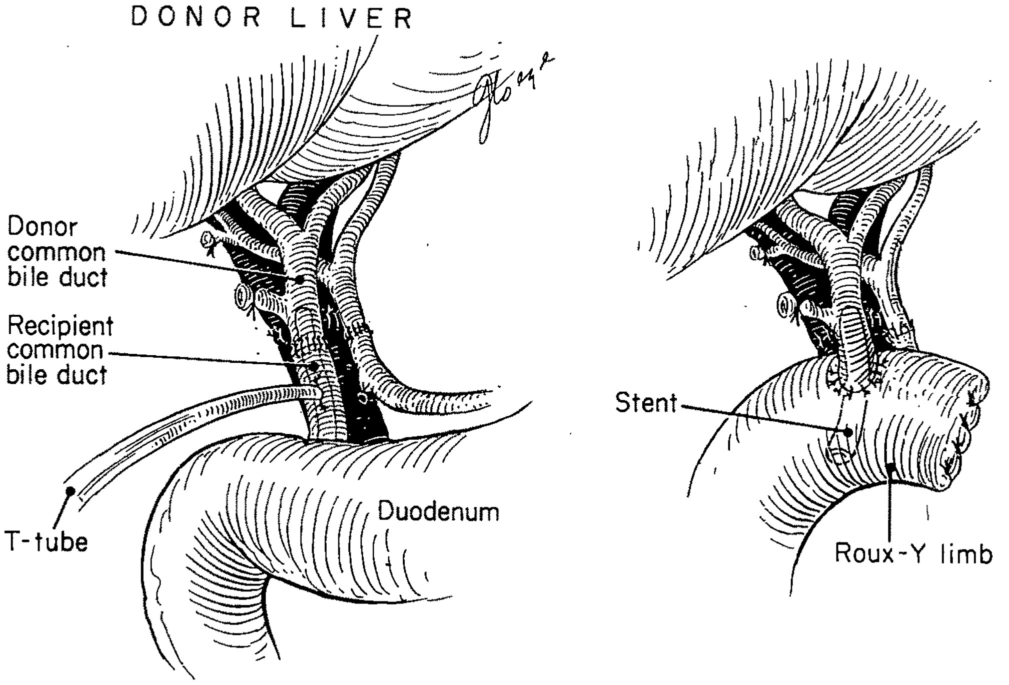

FIG. 4. Biliary reconstruction by choledochocholedochostomy with T-tube stent (left) or Roux-en-Y choledochojejunostomy with indwelling straight stent.

#30), one as part of a gastric devascularization for bleeding (OLT #15), and the other to facilitate ventilator weaning made difficult by diaphragmatic pressure from the large spleen (OLT #26). One adult had splenectomy for a lacerated spleen (OLT #52). The first patient had an episode of *Hemophilus influenzae* sepsis 5 months after transplantation that was treated successfully, the second patient has done well for 15 post-transplant months, and the other three patients (OLT #26, OLT #15, OLT #52) died of sepsis and liver failure in the postoperative period.

Immunosuppression and Rejection

Cyclosporine and prednisone were used as the principal regimen. Before operation, the patients received cyclosporine, 17.5 mg/kg orally (5 mg/kg intravenously if oral intake was not possible), and methylprednisolone, 20 mg/kg intravenously. After transplantation, they received cyclosporine, 5 mg/kg/day intravenously, in divided doses until oral intake was adequate, then 17 mg/kg/day orally in divided doses. There was usually a 5–7 day crossover period during which both intravenous and oral cyclosporine were given to ensure adequate blood levels. Cyclosporine levels (plasma radioimmunoassay) were followed daily and dosages adjusted to maintain a trough level of 200–300 ng/mL and for renal dysfunction. Intravenous methylprednisolone dose after operation was 10 mg/kg/day initially, tapered to 0.3 mg/kg/day by the end of the first week. Prednisone was given by mouth when oral intake resumed.

When acute rejection was suspected based on clinical findings or on abnormalities in tests of liver function or liver biopsy, an algorithmic approach was used. Intravenous methylprednisolone, 20 mg/kg, was given for 2 days. If a response was seen, the patient was returned to maintenance cyclosporine and methylprednisolone. If there was no response, a 5-day methylprednisolone recycle was begun, 30 mg/kg on the first day, then 10 mg/kg tapered to 0.3 mg/kg. If this did not reverse rejection, the patient was enrolled in a protocol to evaluate OKT3 monoclonal T-cell antibody.[16] Retransplantation was considered for failure to respond to OKT3. Responders received azathioprine, 1–2 mg/kg/day.

Virtually all patients had at least one mild rejection episode treated with a steroid pulse. Twenty-one patients refractory to these measures were treated on the OKT3 monoclonal antibody protocol, 17 with acute rejection during their initial hospitalization and four with chronic rejection who were readmitted to the hospital. Thirteen patients had a complete response with normalization of liver function, eight had a partial response, and two patients died of ongoing sepsis. Two patients eventually required retransplantation, one for hepatic artery thrombosis and one for chronic rejection. The remaining 17 grafts (76%) are currently functioning satisfactorily. Measurements of total bilirubin, SGOT, and SGPT were found to be reduced significantly after

OKT3 therapy. Survival of patients receiving OKT3 was 86%.

Percutaneous liver biopsies were performed on 114 occasions in 57 patients. Half of the biopsies showed rejection and half showed other phenomena such as ischemic injury, viral hepatitis, or cholangitis. Liver biopsy was a safe procedure: one bleeding episode requiring transfusion was the only complication. The results of biopsy data have been reported previously.[17]

Results

Postoperative Course

Average length of hospitalization for the 63 patients who survived after transplantation was 50 days (range: 18–155 days). Certain complications were seen on a recurring basis.

Seizures. Eighteen of 83 patients (22%) had grand mal seizures. In only one of these patients was a focal neurologic deficit found. This was a 2-year-old child in stage IV hepatic coma in whom postoperative sepsis developed before brain herniation and death. In the other patients, seizures were multifactorial. However, in six of 10 adults and in five of eight children, magnesium levels were below 1.6 mg/mL. Mean trough cyclosporine level of patients who had seizures was 405 ng/mL. No other significant abnormalities in electrolyte, glucose, or osmolar balance were found. Thirteen of the 18 patients survived to leave the hospital, and none had neurologic sequelae.

Pulmonary complications. Twenty-one patients (25%) required mechanical ventilation for more than 5 days after operation. Causes included limited nutritional reserve, diaphragmatic compression by abdominal viscera (both before and after transplant), and diaphragmatic paralysis. Paralysis of the right diaphragm occurred in 12 patients. This was a chest x-ray finding that was confirmed with real-time ultrasonography and is probably the result of a clamp injury to the phrenic nerve when obtaining control of the suprahepatic vena cava cuff. Transient right-sided pleural effusions occurred in 45 patients and right upper lobe atelectasis occurred in 36 patients.

Renal failure. Virtually all patients exhibited oliguria in the first 24–48 hours after transplant, and 50 (60%) had elevations of serum creatinine levels to twice the preoperative value. Of four children (OLT #19, 23, 26, 75) requiring hemodialysis because of severe oliguria with resultant fluid overload, hyperkalemia, and acidosis, all ultimately died of sepsis and organ failure (one of these children, OLT #75, had fibrinolysis as the cause of her organ failure). Seventeen adults required hemodialysis in the perioperative period, and six died.

TABLE 4. *Infectious Complications in 42 of 83 Patients (51%)*

	No. of Episodes
Early	
Bacterial	34
Viral	22
Fungal (Candida)	15
Late	
Viral	7
Bacterial	10

Early = less than 2 months.
Late = greater than 2 months.

Infection. Patients were scrutinized closely for infectious complications. All received oral antibiotic bowel preparation (neomycin and erythromycin base), nystatin and chlortrimazole antifungal prophylaxis, and perioperative parenteral antibiotic therapy with ampicillin and cefotaxime for 72 hours. Antiviral prophylaxis (Acyclovir®) was not used. Postoperative infections occurred in 42 patients, or 51% (Table 4). Half of the patients who died had at least one infection identified. A detailed analysis of our infectious complications was the subject of another report.[18]

Hypertension. Systolic and diastolic hypertension was a frequent finding in the children. This is perhaps an effect of cyclosporine and steroids. Thirty-three children (87%) required intravenous antihypertensive therapy, and discharge medications included antihypertensives in 16 of 31 patients who left the hospital. Only eight of 33 adults were discharged requiring antihypertensives.

Survival

Of the 83 patients, 63 are alive (76%; adults 72%, children 80%). The 1- and 2-year actuarial survival rate is 73% and 73% respectively (68% and 68% in adults, 78% and 78% in children) (Fig. 5). Of 43 patients transplanted in the past year, 38 are alive (adults 88%, children 89%). Causes of the 20 deaths are shown in Table 5.

There were no operative deaths. Three late deaths were due to recurrent tumors. Three patients died in the early postoperative period; one of a ruptured splenic artery aneurysm, one of pulmonary hemorrhage and resultant respiratory failure due to an episode of primary fibrinolysis that occurred shortly after liver reperfusion, and one of ongoing bleeding after transplantation for alcoholic cirrhosis. The remaining 15 deaths occurred within 4 months of transplantation and were due to varying combinations of sepsis, organ failure, rejection, and bleeding.

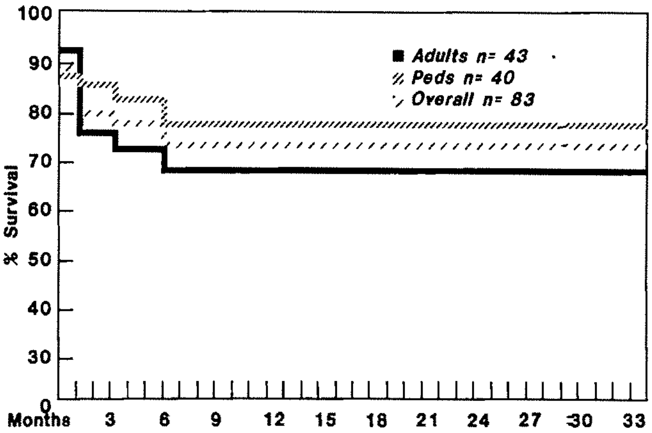

FIG. 5. Acturial survival curve of all patients undergoing liver transplantation. Computed by Kaplan-Meier method.

Of four patients who received an ABO incompatible liver, three are alive and one died. This patient (OLT #26), with blood type O, was retransplanted with a type A liver and died of sepsis and liver failure. One patient (OLT #41) with blood type A was retransplanted with a type B liver due to emergent circumstances. She had a second retransplantation with a type A liver 7 months later because of chronic rejection and is now well. The other two patients (OLT #56 and #82), both blood type O, received type B livers and have normal liver function at 8 months and 2 months, respectively. Of 21 patients with a compatible, yet not identical, ABO match, eight patients died. The overall graft survival is significantly lower at both 1 and 2 years in ABO nonidentical matches *versus* ABO identical matches (Fig. 6).

Routine cytotoxic antibody testing against donor lymphocytes was performed but did not play a role in donor selection. Graft survival *versus* reactivity to B-cell warm, B-cell cold, and T-cell warm antibodies was evaluated. No statistical difference in survival was seen, although there was a suggestion of lower 1-year graft survival in those patients with greater than 10% T-cell warm antibodies compared with patients with less than 10%; graft survival was 50% *versus* 65.4%, respectively.

Retransplantation

A total of 17 retransplants were performed in 83 patients (20%). Four patients had retransplantation twice. Overall retransplant survival was seven of 13 patients (54%). Survival of retransplantation for hepatic artery thrombosis, rejection, and primary nongraft function were 100%, 57%, and 33%, respectively (Table 6).

TABLE 5. *Mortality in 20 of 83 Patients*

OLT #	Disease	Cause of Death	Time Post-transplant	Comment
1	Hepatic schwannoma	Recurrent tumor	4 months	
4	Hepatocellular carcinoma	Anoxic brain death	32 days	Retransplant
5	Budd-Chiari	Disseminated herpes	28 days	1st Retransplant primary nonfunction 2nd Retransplant for suspected rejection
8	Idiopathic cirrhosis	Chronic rejection/sepsis	3 months	
11	Tyrosinemia with hepatoma	Recurrent tumor	10 months	Tumor involved hepatic veins
13	Primary biliary cirrhosis	Liver failure/sepsis	12 days	
15	Primary biliary cirrhosis	Sepsis	49 days	
16	Biliary atresia	Disseminated adenovirus	17 days	Retransplanted for suspected rejection
19	Biliary atresia	Fungal sepsis/liver failure	7 weeks	
23	Biliary atresia	Fungal sepsis	25 days	Extensive previous biliary surgery (12 operations)
24	Chronic active hepatitis	Chronic rejection	2 months	Refused retransplant
26	Biliary atresia	Sepsis/liver failure	4.5 months	Retransplant/hepatic artery thrombosis
28	Chronic active hepatitis with hepatocellular carcinoma	Recurrent tumor	9.5 months	
29	Chronic active hepatitis	Fungal sepsis	27 days	Retransplant
31	Acute hepatitis A	Brain dead	10 days	Did not regain consciousness
46	Sclerosing cholangitis	Sepsis, liver failure	2.5 months	Retransplant twice for nonfunction
51	Alpha-1-antitrypsin	Ruptured splenic artery aneurysm	5 days	Normal liver function
52	Alcoholic cirrhosis	Coagulopathy/ARDS	3 days	
61	Sclerosing cholangitis	Pseudomonas pneumonia	37 days	Normal liver function
75	Tyrosinemia	Intrapulmonary hemorrhage	2 days	Primary fibrinolysis

Risk Factors

A number of pre-, intra-, and postoperative factors were assessed to determine if variables predictive of early (2 months) postoperative survival could be identified. In addition, a group of pre- and intraoperative factors were analyzed to seek a correlation with blood loss. Factors assessed included age, diagnosis of liver disease, previous operations, liver chemistries, encephalopathy, donor liver ischemia, rejection, and need for dialysis. The unpaired Student's t-test was used to compare means and chi-square analysis to compare proportions. Overall 2-month survival was 67 of 83 patients (81%). None of these factors showed statistical correlation with survival except the need for dialysis and severe rejection (requiring retransplantation). Only 11 of 21 patients (43%) of those requiring dialysis survived *versus* 56 of 62 patients (90%) who did not ($p < 0.0005$). In patients who have severe rejection, five of 11 (45%) survived *versus* 42 of 52 (81%) with mild rejection and 20 of 20 (100%) with moderate rejection ($p < 0.01$).

Age over 50 years and presence of a portacaval shunt significantly affected intraoperative blood loss ($p < 0.02$ and $p < 0.005$, respectively). Blood loss could not be correlated with diagnosis, previous abdominal surgery (including nonportacaval portasystemic shunts), or liver chemistries. Actuarial survival curves of 100 allografts are shown in Figure 7. The three curves illustrate three groups of patients according to intraoperative blood loss; group I, 1–10 units PRBC; group II, 11–30 units; group III, greater than 30 units. One-year graft survival was superior in group I *versus* group II ($p = 0.04$). Although a trend toward improved long-term survival with lower blood loss is evident, this did not reach statistical significance.

Growth and Development

The effects of liver transplantation on growth of 29 pediatric patients was assessed. Mean follow-up was 13.9 months (range: 4–33 months). Average age at the time of transplant was 5.8 years (range: 7 months to 16 years). Percentiles for weight, height, and weight-for-height were calculated before and after transplantation. Results are shown in Table 7.

Most patients exhibited normal or accelerated growth after transplant. The three patients who showed growth failure had been receiving higher than usual steroid dosages for repeated bouts of rejection. The growth velocity index (GVI), or increment of height per year, was also assessed. These results are compared with velocity standards for height based on chronologic age. Twenty-seven (93%) of patients demonstrated a GVI greater than 100 (normal value is greater than 80). GVI before transplant was 79.6 ± 20.78 *versus* 147.4 ± 16.36 after transplant ($p < 0.01$).

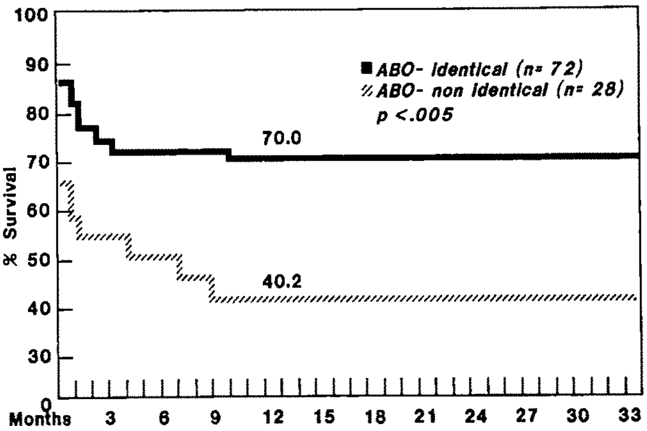

FIG. 6. Actuarial graft survival of ABO identical and ABO nonidentical donor/recipient matches. All grafts included.

The effects of liver transplantation on cognitive and intellectual development are anecdotal at present. Currently we are evaluating our patients with psychomotor tests.

Through December 1, 1986, 29 adults who had transplantation have been discharged from the hospital for a minimum of 4 months follow-up. Twenty of 29 patients (70%) have returned to normal activity or returned to work. Nine patients have improved activity compared with pretransplant status. No discharged patients have demonstrated a regression in functional capability.

Fiscal considerations

The financial burden of the procedure falls to commercial insurance carriers, state-funded medical pro-

TABLE 6. *Retransplantation*

OLT #	Indication	Outcome
4	Rejection	Dead
5	#1—Primary nongraft function #2—Presumed rejection*	Dead
16	Presumed rejection*	Dead
21	Rejection	Alive
26	Rejection	Dead
29	Primary nongraft function	Dead
36	#1—Arterial thrombosis #2—Arterial thrombosis	Alive
41	#1—Rejection (acute) #2—Rejection (chronic)	Alive
46	#1—Rejection #2—Rejection	Dead
54	Primary nongraft function	Alive
78	Rejection	Alive
79	Hepatic artery thrombosis	Alive
80	Rejection	Alive

* Pathologic findings revealed overwhelming viral infection and not rejection.

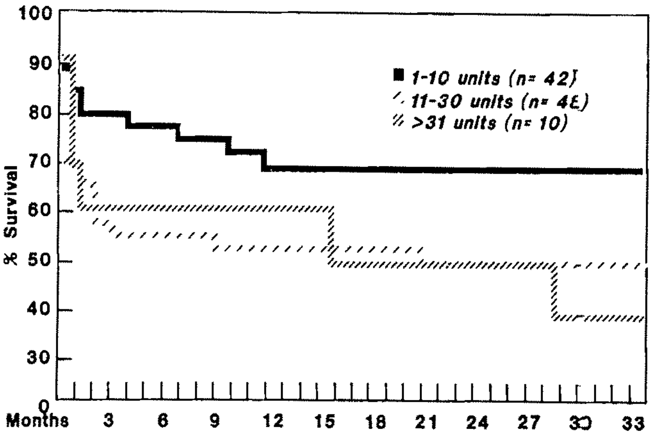

FIG. 7. Acturial graft survival comparing differences in operative blood loss.

grams, or self-payment. At the UCLA Medical Center, guarantee of payment is required before a patient is placed on the active list. Adherence to this hospital policy is mandatory to maintain solvency. Hospital charge for pediatric patients has ranged from $46,000 to $637,000, with a median of $109,000; hospital charge for adult patients has ranged from $66,000 to $609,000, with a median of $138,000. Mean charges for children and adults have been $164,000 and $175,000, respectively.

Discussion

After the National Institutes of Health Consensus Conference on liver transplantation concluded that the procedure should be considered a therapeutic modality in selected patients with end-stage liver disease, a number of centers either expressed intent or initiated programs in OLT. UCLA began its preparation for such a program 6 months before the Consensus Conference. This program was built on a foundation of basic laboratory preparation and cautious early clinical efforts. Expansion was gradual but steady, with 20 OLTs performed in 1984, 38 in 1985, and 53 in 1986. The 100th transplant occurred in the 33rd month of the program.

The protocols for both pediatric and adult patient evaluation and selection have been detailed.[6,7] As our program has evolved, an increasing number of patients are being referred for consideration. The primary reason for this phenomenon is that OLT is now recognized more frequently by both the gastroenterologist and primary care physician as the definitive treatment for patients with chronic liver disease. Rarely is a patient categorically rejected from consideration until a full evaluation is performed. In many cases, patients who might be judged as noncandidates at first presentation have been accepted and transplanted. With improving results, absolute contraindications are decreasing. Although age greater than 55 years was considered a relative contraindication, we and other groups have transplanted patients in the seventh and eighth decades who have returned to productive lifestyles. A recent report[19] suggests no difference in survival of patients over 50 years of age. Although the numbers are small, our results indicate a poorer survival in patients over 50 years of age because of greater blood loss in this group. Our current policy is not to refuse candidacy on the basis of age alone if a thorough cardiopulmonary and renal assessment does not disclose a specific physiologic contraindication.

TABLE 7. *Growth Data in 29 Pediatric Patients*

	Percentile Curves After OLT					
	Weight		Height		Weight for Height	
	N	(%)	N	(%)	N	(%)
Accelerated	25	86	17	59	23	80
No change	4	14	11	38	3	10
Loss	0		1	3	2	10

"Unresectable hepatic malignancy" is one of the most problematic indications for transplantation. Reports from other centers[20] and ours[21] have indicated a 50–70% recurrence rate within 2 years. Moreover, even the most thorough preoperative assessment may not discern the presence of extrahepatic spread, which would preclude a curative operation with total liver replacement. Despite these pitfalls, we have offered transplantation to carefully selected patients with malignancy. Of seven patients transplanted for this indication, five are alive and free of disease from 5 months to 3 years after transplant. In all patients, the quality of life after transplant has offset the uncertainty of tumor recurrence. Adjuvant chemotherapy has been given before and after operation in some patients. Protocols based on increasing experience will be needed to define specific indications for liver transplantation in patients with malignancy.

Liver transplantation in the adult population for chronic active hepatitis, primary biliary cirrhosis, and sclerosing cholangitis is becoming well accepted with patients with end-stage disease. However, as has been pointed out by Neuberger et al.,[22] the timing of OLT is perhaps one of the most crucial issues in the evolution of this treatment.

In our series, we have seen no significant differences in survival after OLT among adults with chronic active hepatitis, sclerosing cholangitis, or primary biliary cirrhosis. This is in contrast to the experience of Starzl et al.,[23] in which patients with cirrhosis secondary to chronic active hepatitis fared worse. The longer follow-up in the Pittsburgh series, with recurrence of chronic active hepatitis in some patients, may contribute to this difference. In a recent report, Demetris et al.[24] found a 100% recurrence of antigen positivity after 2 months in patients transplanted for hepatitis B. In our series, recurrent B antigen positivity developed in 50% of patients despite the administration of hyperimmune anti–B-gamma globulin during the anhepatic phase. However, no patients thus far have had histologic evidence of recurrence of chronic active hepatitis up to a 2-year follow-up.

The results of liver transplantation in children have been generally superior to those for adults.[23] Not only is the pediatric patient more resilient to the rigors of transplantation, but there appears to be a lack of influence of the primary disease on the eventual outcome after OLT. This is evident both in children with biliary atresia and with inborn errors of metabolism. Actuarial survival in each group at 2 years is close to 80%. Because of the favorable statistics, it is rare to reject a child for transplantation despite substantial preoperative risk factors. In many cases, the transplant procedure will be technically much more demanding after multiple attempts at portoenterostomy revision, yet this has not proved to be a significant deterrent to success.

It is accepted that for OLT to be successful, the operation must be technically perfect. This assumes a well-preserved and immediately functional graft, an expeditious and blood-sparing recipient hepatectomy, and a precise anastomotic reconstruction of vascular and biliary components. Our techniques in these phases of the operation have been based on those described by Starzl et al.,[9] modified and adapted to our own team.[11] Flexibility in response to changing demands of the operative circumstances is essential to the conduct of the procedure. This is illustrated by our approach to arterial reconstruction, in which five different methods have been used. Using this adaptable strategy, we have achieved a 95% patency rate, which is comparable to the Pittsburgh series (93%).[25] There have been no arterial thromboses in our adult series. Our methods of biliary reconstruction have been choledochocholedochostomy or Roux-en-Y choledochojejunostomy. The complication rate has been 24%, but no complications have resulted in death of any patient. This figure, although higher, is similar to the 13.2% complication rate reported by Lerut and colleagues[26] in 393 grafts.

The use of cyclosporine has been the single most important factor in the improved survival for OLT. In the early series (1963–1979) reported by Starzl et al.,[3] less than one third of patients lived 1 year. Now, it is routine for 1-year survival to be twice that figure. An important adjuvant to the cyclosporine/steroid immunosuppression regimen has been the introduction of OKT3 monoclonal antibody to treat acute allograft rejection.[27] Our experience has mirrored the multi-institutional trial[28] in that all of our patients have had either a partial or complete reversal of rejection. The results of OKT3 have been so favorable and its lack of nephrotoxicity is so appealing that a trial for prophylactic use has been initiated.

An actuarial survival rate of 73% at 1 and 2 years after OLT in our series has been comparable with outcomes reported by others.[23,29,30] Also, the pediatric population has fared better than the adults, with a 2-year actuarial survival rate of 78% *versus* 68% for adults. It appears that the 9-month survival is most important, since late attrition after this time is significantly decreased. Factors that influence late mortality include recurrence of primary disease, chronic rejection, and late infectious complications. In our patients, recurrent tumor and infection were the predominant causes of late death.

The causes and predictors of early mortality after OLT have been studied extensively by Shaw et al.[31] In a similar analysis of our patients, only need for dialysis or severe rejection predicted early mortality. However, intraoperative blood loss that exceeded 10 units resulted in a statistically lower 1-year survival than a blood loss of less than 10 units. No difference was found in blood loss from 10–30 units or greater than 30 units. This is in contrast to the report of Shaw et al.[31] that demonstrated superior survival in the group requiring 0–35 units *versus* 36–100 units *versus* greater than 100 units, respectively. Our data support the observation that of all factors studied, low intraoperative blood loss correlates most strongly with early survival.

Although recent experimental data by Knechtle and co-workers[32] demonstrate the occurrence of hyperacute hepatic allograft rejection in sensitized recipients, we have not observed graft survival to be decreased significantly in patients with preformed cytotoxic antibodies. However, in our analysis of graft survival, nonidentical ABO-matched organs faired worse than identically matched ones. A much larger analysis of this has been presented by Gordon et al.[33] with similar results.

Despite the major role that cyclosporine has played in the improvement of patient survival after OLT, there is the continued threat, particularly in the first 3 months, of irreparable allograft dysfunction. Retransplantation is the only hope for these patients. We have maintained an aggressive posture in this regard, with 17 of our first 100 cases being retransplants (20%). Best results are obtained if the indication for retransplantation is arterial thrombosis or early acute refractory rejection. Primary graft nonfunction generally has a poorer prognosis both in our series and that of others.[34]

Extrahepatic postoperative complications after OLT are expected and must be anticipated. An operative endeavor of such magnitude performed on a compromised host who is then immunosuppressed cannot be expected to be free of problems. Infection, renal failure, pulmonary, gastrointestinal, and neurologic complications occurred singly or in combination in approximately 60% of patients in this series. Notably absent, except in terminal patients, were cardiac complications such as arrhythmias, congestive heart failure, or myocardial infarction. Neurologic complications were unexpectedly frequent with grand mal seizures occurring in 22% of patients. In most patients, seizures were associated with low magnesium and elevated cyclosporine levels. The relationship between hypomagnesemia and cyclosporine-induced neurotoxicity has been previously reported by Thompson and co-workers.[35] None of our patients exhibiting seizures had permanent neurologic deficits.

Return of functional status in adults and growth and development in children are important parameters in the ultimate assessment of the benefits of OLT. Seventy per cent of our discharged adults have returned to gainful employment and virtually complete rehabilitation to their premorbid condition. The remainder have shown significant improvement, without a single patient demonstrating regression. More objective criteria are available for evaluation of the success of OLT in pediatric patients. When growth and development were monitored, 59–86% of our children demonstrated acceleration of weight, height, or weight-for-height ratio.[36] Gartner et al.[37] analyzed a similar series of 22 patients and found accelerated growth in 11, normal growth in 10, and growth failure in only one.

Liver transplantation is a procedure in evolution. Through the principal pioneering efforts of Starzl et al.,[1] this therapy may now be offered to patients in a logistical scope that was barely thinkable less than one decade ago. The cost of this procedure is high. However, the operation has now provided successful treatment and cure of diseases heretofore considered dismal or hopeless. As a consequence of transplant-related research, our basic understanding of hepatobiliary physiology, pathology, and surgery have expanded dramatically. Fertile areas for future study include preservation and protection of the ischemic liver, the molecular basis of acute and chronic rejection, multiple organ transplantation, and new immunosuppressive agents.

Acknowledgments

We thank the many individuals who have contributed faithfully and unselfishly to the Liver Transplant Program at UCLA: Tatsuto Ashizawa, M.D., Debra Besbris, R.N., Leslee Boyd, M.S.W., Lisa Conti, Marilyn P. Hoff, R.N., Barbara J. Nuesse, R.N., Deanna Ruttenberg, and Amy Sackman.

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DISCUSSION

DR. JOHN S. NAJARIAN (Minneapolis, Minnesota): I would like to congratulate Ron Busuttil on an excellent paper, which is both beautifully illustrated and presented. In addition, this paper chronicles the establishment of a new liver transplant unit, and I believe that similar results are now being achieved at other units.

I had the privilege of reading this manuscript before, and I have a few comments and a few questions.

Dr. Busuttil has noted a high incidence of rejection. He is quoted as stating that 100% of the patients had at least one rejection episode and several had more.

(Slide) At this point in our own program, we have carefully followed a program that was started in Minnesota using triple therapy, as we reported 3 years ago in our kidney transplantation program. You can see that with triple therapy, which is azathioprine, prednisone, and cyclosporine, we had results with our HLA-matched relatives of 100% over 1 year, 95% with mismatched-related donors, and approximately 85% using cadaver kidneys.

(Slide) If we then turned our attention to cardiac transplantation, again using triple therapy, we have achieved about 95% graft survival in 73 cardiac transplants over the past 2 years.

(Slide) Finally, with liver transplantation we now are looking at approximately 76% patient survival, which is similar to what Dr. Busuttil showed. However, our retransplant rate is only 3%, not 20%, as presented, so that basically our survival statistics here not only represent patients but they represent graft survival as well. Therefore, we believe that triple therapy can save some of the high retransplantation rates, and as was pointed out by Dr. Busuttil, those patients fare less well, about 54%, when they require retransplantation.

If we look at our statistics in liver transplantation, we see that in the very young, under the age of 10, we do well (85%), and between 10 and 18 years of age, we also have excellent survival statistics. However, our adults over the age of 19 have a graft survival of around 70%, results that are not too dissimilar from those shown by Dr. Busuttil.

The second point concerns arterial problems. We found that the only arterial problems we observed are primarily seen in our pediatric population, in which we noted five thromboses. All occurred when we used an aortic-to-aortic anastomosis for a total rate of about 8%; therefore, we believe that this type of arterial revascularization should be avoided if possible. Currently, we no longer do aortic-to-aortic anastomoses.

I would like to ask a few questions. There was one case that came up in the manuscript in which a splenectomy was done and gastric devascularization was performed for esophageal bleeding. Was this done because of an occlusion of the portal vein, and if so, how was the diagnosis made?

Secondly, Dr. Busuttil reported an infection rate of 51%. This is about right, but the concern that I had is if this rate is any higher in the group of steroid-resistant rejections that required OKT3 or was it similar in both groups? In other words, was it possible that OKT3 added to the higher infection rate compared with those patients who just received steroids alone?

The third question concerns blood loss. Dr. Busuttil reported that there was no good correlation of blood loss and mortality noted. Under 10 units there was a good correlation with survival; from 19 to 30 units, Dr. Busuttil did not have a good correlation; above 30 units there was no correlation. My question is since we found a very close correlation with blood loss and survival statistics, are your results affected primarily by pediatric cases? Certainly, a 10-unit blood loss in a small infant is quite different than a 10-unit blood loss in an adult.

My final two questions are: virtually all of the patients had oliguria, and from that group, 60% had a doubling of their serum creatinine level. Dialysis was required in 25% and of 21 patients, 10 died who required dialysis. Six of 17 adults died requiring dialysis. We do not use a veno-veno shunt. We have not found it necessary in any of our patients, and we wondered if with the lower renal dysfunction rate, which is supposed to be one of the advantages of the veno-veno shunt, why do you think you had this high rate of oliguria and eventually renal failure? Is there some problem here that we do not recognize, because certainly, without the use of the veno-veno shunt, we have had only 6% of our patients require dialysis.

We believe that it is important to keep the operation short. Our mean operative time is 6 hours or less, and we believe that elimination of the use of the veno-veno shunt is helpful in that regard. I would be interested in Ron's comments.

Finally, Dr. Busuttil reported that 22% of his patients had grand mal seizures. This occurred in 18 patients. Five of these patients died. We saw this complication in only 5% of our patients.

We started using Decadron before operation, during operation, and for the next 72 hours. Since that time we have not had a single episode of seizures. Have you tried using Decadron, or what have you done to try to decrease the number of seizures in your patients?

DR. G. KLINTMALM (Dallas, Texas): I truly enjoyed this paper very much. The results that have been achieved at UCLA are absolutely staggering.

At Baylor in Dallas we have our own program since 2 years back, and we have performed about 95 transplants with a survival rate of 85%. I have one comment and one question.

We have routinely measured the hepatic and arterial blood flows in all our patients, and as a consequence of the findings, during the transplant surgery we have revascularized three arteries and one portal vein. I believe that this technique may help to prevent some of the unexpected problems such as vascular thrombosis we may find after operation.

Despite this, we have found three arterial thromboses, and they have been caused twice by acute angulation of the artery and once by a recipient artery intimal dissection.

The three patients were rushed to surgery where revascularization including thrombectomy and arterial reconstruction was carried out. The outcome of these patients was satisfactory. I propose that the concept that we have had up to this time that we should go to retransplantation in hepatoarterial thrombosis is not valid any more.

My question is the same as Dr. Najarian's. You have an extremely high rejection rate. We have a 72% rejection rate that has been histologically verified. I would like to know on what ground you made your diagnosis. Was this done by only clinical symptoms or were the rejections verified by other means?

DR. S. IWATSUKI (Pittsburgh, Pennsylvania): I would also like to congratulate Dr. Busuttil and the UCLA liver transplant team on their excellent results and thank them for the opportunity of reviewing their manuscript.

It seemed like only a few months ago rather than years that Dr. Jim Maloney, the former Chairman at UCLA, sent Dr. Busuttil and his colleagues to Pittsburgh on sabbatical before their first clinical trials of liver transplantation in 1984.

I would like to present our own experience in Pittsburgh to show that the series at UCLA is one of the best.

We have performed more than 1000 liver transplantations with cyclosporine and steroid therapy since 1980, but for this discussion I reviewed our first 100 patients during the 33 months from March 1980 to December 1982, 4 years before the UCLA series.

During this period the proper use of cyclosporine still had to be learned. Cyclosporine blood level monitoring was not available. The venovenous bypasses had not been invented and the monoclonal ALG was not available.

With this primitive situation 60 of our first 100 patients lived for at least 1 year and 50, exactly one half of the patients, are still alive and well as of April 1987, between 4.5 and 7 years after liver transplantation.

The causes of the 50 deaths have usually been too complex for simple classification. However, 14 patients died as a result of surgical technical errors or complications that could have been minimized if modern surgical techniques had been applied. Ten patients died of infectious complications and nine died of graft rejection or complications after retransplantation.

Other main causes of death included recurrent hepatic malignancy, recurrent hepatitis B, recurrent Budd-Chiari syndrome, and lymphoproliferative disorder.

The complication rate of the UCLA series seems to be higher than ours. Our biliary complication rate after duct-to-duct anastomosis with a "T" tube was 5% and that of duct-to-Roux-en-Y jejunum was 6%.

I realize that it is difficult and sometimes even meaningless to compare the results obtained from different clinical populations and especially during different time periods. Nevertheless, the results achieved by the UCLA group are superb. I would like to ask Dr. Busuttil a couple of questions.

How many patients were not accepted as candidates for liver transplant at UCLA and what were the reasons? In other words, what are the acceptance and nonacceptance criteria during that reported period and currently?

I congratulate again the UCLA liver transplant team on their excellent results and thank the members of the society for this privileged opportunity for discussion.

DR. PAUL S. RUSSELL (Boston, Massachusetts): Dr. Busuttil kindly invited me to discuss his interesting paper that I have read. It is a good paper. It is full of interesting information, and there are many things that one could discuss in connection with it. It bears out his conclusions that with the right people and in the right place, you currently can do very well with liver transplantation. His survival rate is, of course, commendable, as it includes all comers, and there are indications in the paper that it is improving nicely.

I believe his conclusions also bear out the impressions of the NIH Consensus Conference on Liver Transplantation in 1983, which suggested that the time had come for cautious peripheralization of this damanding procedure throughout the United States.

It is interesting to recall that at that time a number of observers told us that we should be randomizing these patients and that was something we did not accept. We did not do so because they are selected for having the best markers we know for impending death.

Now, with the results that Dr. Busuttil and others are achieving, there will be a great tendency to push out the envelope of indications for this operation in all sorts of different directions. Remembering that we are all using the same restricted resource of donors, this is something that we should do with great care. I believe that a place for randomized studies could be found in this difficult area, particularly if we are going to push it back to earlier stages where impending death is not obviously present. Of course, if we take patients earlier, we will get better survival, and we will probably have a less expensive operation.

There is much to be learned about liver transplantation. The question had been raised already in this discussion about how one diagnoses rejection. We do not know exactly how to diagnose rejection yet.

There is an NIH study that has been instituted called the National Liver Transplant Data Base, which is a multiinstitutional effort, and from that perhaps some new information will come in part.

I have a few questions for the UCLA group which has achieved such fine results. It is interesting that they had bile peritonitis as commonly as they did. This is something we did not see. I am curious what their plans are in the future about this. Did the tubes come out too early or was there anything else you can obviously see that might be avoided in the future?

Secondly, the secondary effects of cyclosporine, I believe, are fairly prominent in your patients. The early renal function has been referred to. There were a number of patients who had seizures, and in fact, 22% had neurologic symptoms. In that group the blood levels were 405 ng/mL, which is a bit high.

Your standard maintance dose of cyclosporine seems to be around 17 mg/kg, which I would have said is a bit too high particularly with the triple drug therapy that John Najarian referred to. I am wondering about the cyclosporine dose as well.

The retransplant rate is an interesting question. This is a complicated issue. There are many things involved in the retransplant rate that John referred to as well. A rate of about 20%, which you have had, is fairly common. It is higher than what we have encountered, and I only raise it here for one final question.

With 54% survival, which is very good for retransplant rates, you do have the issue about who gets a liver. In other words, here is a patient who need a transplant and you have got a primary liver transplant success rate that is higher. What is your thinking about this? It depends, of course, entirely on the number of livers available.

Therefore, my question is: how are you doing for donors on the West Coast?

A final comment, if I can make it, is a criticism of transplantation usage, which is widely in vogue. This is the constant referral to "patients transplanted," as in "we transplanted 20 patients." We transplant organs, not patients, of course.

DR. C. BROELSCH (Chicago, Illinois): For everyone who has undertaken the task of establishing a liver transplant program, the work and results of Dr. Busuttil and colleagues seem to be admirable and the authors need to be congratulated.

Their report exemplifies and heralds a new step in the evolution of liver transplantation. That is the development of regional programs, their necessity and their goals. Within a short time the number of patients requiring liver transplants will exceed a few thousand per year in the United States. Careful estimates are between 15 and 20 candidates per one million inhabitants per year.

It is mentioned correctly that 50 centers have been prepared or are being prepared to start a liver transplant program. However, up to now, fewer than five centers have performed around 100 procedures or more than 50 procedures per year within the last 2 years. Certainly others will catch up, but the development of regional centers should not become a race for numbers. Regional responsibility, to cite Dr. Starzl, is meant to serve an area, its patient population, enhance experience with liver transplant, and educate the medical profession by offering this new treatment.

A huge number of patients are now seen by many liver transplant specialists and selections are made on criteria that are not yet defined among the hepatologists and surgeons. Consequently, it is extremely difficult to compare overall survival rates, although this is exactly what is being done currently among the new centers and the "standard center," Pittsburgh.

Regional centers, at least initially, as I believe, have to take patients with extreme high risks who cannot be transferred and should not be transferred to unload a problem on someone else's responsibility, not to mention survival statistics.

Apparently the UCLA group paid the initial tribute when 15 of their first 40 patients died compared with only five of the subsequent 54.

The quality of the program in the long run is what counts and obviously makes up for these losses.

The UCLA group presents excellent results and particularly in the pediatric group, which have been favorable in many centers. From my own previous experience at the University of Hannover, Germany, results have always been above the 70% range.

However, one has to be aware that up to 50% of the children, although accepted for transplantation, die while they are waiting for a transplant. This is particularly true for children younger than 2 years, and in the UCLA experience the average age of pediatric recipients who were accepted and died before transplantation was 9.5 months.

The very small children are the ones with the highest risk for hepatic artery thrombosis or receiving a bad functioning graft, because some potentially damaged donor organs are used to overcome scarcity of small pediatric organs.

In our first year we had rather surprising results, while we have seen 36 children with 65% younger than 2 years. Twenty-seven received a transplant, whereas six were not candidates and could be treated otherwise. Only three died while they were on the waiting list.

(Slide) We paid a price for that because our survival rates in the first year barely hit 55%, and that includes patients with one intraoperative death, early transplant failure, and a small percentage of retransplantation. It includes the attempts of performing reduced-size liver organs that are obtained from adults for those children. However, becoming more selective, although not exclusive, immediately as of May 1986, with the subsequent 17 cases, one can accomplish >80 percent. That includes a couple of segmental grafts from adult donors as well.

The UCLA presentation has strongly emphasized that operative procedures, patient monitoring, including immunosuppression therapy, have become fairly standardized, thus making liver transplantation a safer procedure for the patient.

Since I had the privilege of reviewing the manuscript, I would like to add three questions: would you elaborate more, Dr. Najarian asked this question before, on the high incidence of convulsions. We have seen this only in patients who were fluid overloaded and required dialysis after surgery. I wonder if this is a pure fluid overload effect rather than a pharmacologic effect on cyclosporine A or the chemical carrier substances that are histamine releasers.

The second question is, from what I read in your manuscript, that nine patients had peritonitis after removal of the "T" tube. We have had almost the same experience and since then in the subsequent 27 adults, we abandoned using a "T" tube and had only one patient with mechanical obstruction, although not related to the anastomosis. If you have bleeding cut edges of the duct, one can perform a safe end-to-end anastomosis with PDS or Dexon. I wonder what the logistics or the necessity for the "T" tube are, to really put them into place any longer.

The last question is about the hepatic artery thromboses you observed. Have they always been in association with a rejection? Have they been related to a bad functioning graft, or is this an effect caused by corticosteroid administration during rejection in the patient?

We have only seen thromboses in the pediatric group as you did and only in combination with high corticosteroid treatment.

DR. W. MILLIKAN (Atlanta, Georgia): The Emory group, like the other people who had the opportunity to review this manuscript, congratulate the UCLA group for this fine paper and record. For those of us who have just initiated liver transplantation, it is a standard of excellence that we will try to emulate.

I have specific questions regarding the high incidence of acute tubular necrosis or need for dialysis since this perioperative variable was the only predicter of short-term survival. Much has been said about that already by Dr. Najarian and others.

Ron, do you really believe this was related to cyclosporine or was it a function of pre-existing disease, *i.e.*, functional distribution of volume hepatorenal syndrome?

Secondly, did you use acute dialysis? I cannot tell from the manuscript, or was it ultrafiltration because of the massive overload that frequently accompanies these patients in the immediate postoperative period?

Third, have you ever used peritoneal dialysis in this setting? We recently had a patient in whom 7 days after her transplant, had occlusion of both the hepatic artery and portal vein accompanying acute rejection. We were able to maintain this patient for 36 hours with peritoneal dialysis until we could harvest and retransplant the patient.

DR. RONALD W. BUSUTTIL (Closing discussion): I would like to thank all of the discussants for their comments and questions.

Dr. Najarian, we have been using triple therapy more frequently as I outlined in the slide showing our OKT$_3$ results. Approximately 40% of patients currently receive low-dose cyclosporine, Imuran®, and steroids. All patients who are treated with OKT$_3$ or ATG for rejection are maintained on chronic triple therapy. We have an impression that the use of three drugs has lowered our incidence of rejection, but we have not yet critically analyzed this.

Regarding the incidence of infection after OKT$_3$ we have not found an increase in bacterial or fungal infections in those patients who received the monoclonal antibody *versus* those who did not. However, it is my impression that there is a higher incidence of CMV infection in those patients treated with OKT$_3$.

Renal failure after liver transplantation is indeed a crucial issue since it forbodes so poorly for the patient. There is no question that if dialysis is required in the early postoperative period that mortality will be higher. In our experience 43% of those requiring dialysis died *versus* 10% of those who did not.

Renal failure in these patients is multifactorial. It is difficult, except in the rare patient, to identify one etiologic factor. Cyclosporine clearly plays a part; however, this is only one facet of a scenario that includes multiple blood transfusions, sepsis, nephrotoxic antibiotics, and perhaps most importantly, the presence of preoperative renal failure. In our series over 60% of the patients who required dialysis after operation were in renal failure before operation.

Our view on venous-venous bypass is that it is an important adjunct to the intraoperative management of adult patients. We routinely clamp the suprahepatic vena cava, with volume loading as a trial; however, this maneuver was tolerated in only 44 of the 100 transplants. By tolerated, I mean maintaining a blood pressure within 15 mmHg of preclamp levels. Venous-venous bypass decreases blood loss by decompressing the portal and caval systems. It only takes us about 30 minutes more to place the patient on bypass, and we are comfortable with this technique.

Like renal failure, the cause of postoperative seizures is multifactorial. An analysis for risk factors for the development of postoperative seizures revealed that two variables were apparent in most patients: one, low magnesium levels, and two, high cyclosporine levels. This has been reported by other groups, particularly with heart transplants. Patients in our series who had seizures had a mean cyclosporine level of 400 and a magnesium level less than 1.6. We routinely maintain cyclosporine levels at the 200–250 range and magnesium levels around 2.

We have not used Decadron since all patients are receiving steroids. Only a few of the seizure patients were fluid overloaded and I doubt that volume status contributed to their seizure disorder. None of the patients in whom grand mal seizures developed had long-term neurologic sequelae, and we only had one death of that group, which was not a neurologic death.

Dr. Klintmalm, we have had no venous thrombosis, either portal or vena caval. We are now in the early phases of using duplex scanning to determine arterial patency, and we believe that this will be a very useful modality. Currently, any patient with suspected arterial thrombosis undergoes angiography. We have not had arterial thrombosis in adults; all have occurred in children. In two patients we attempted thrombectomy of the hepatic artery and neither of these were successful. Both patients required retransplantation.

The diagnosis of rejection after liver transplantation is not easy. Generally speaking it is a diagnosis of exclusion. We must first rule out a technical problem such as thrombosis or bile duct obstruction, then rule out infection and drug toxicity. Exclusive of these, biopsy confirmation is essential but not totally diagnostic. We have some ongoing studies with monoclonal identification of T-cell subsets, but the results of these are too preliminary to discuss.

Dr. Iwatsuki, clearly we are indebted to Dr. Starzl and yourself for your counsel and guidance. How well I remember the multiple phone conversations on our first few transplants in which I sought your advice and encouragement and I am very grateful for that.

In regard to the numbers of patients who are transplanted *vis a vis,* those who are evaluated I can give you some rough figures. About one of three children will die before we transplant them and one of every five adults will also die before a donor is found. Roughly 15% of the patients who are evaluated are rejected for transplantation. The reasons for this are multifactorial. In many patients, we considered the stage of their disease too early. In some, we did not consider it an appropriate indication.

I believe it is important to point out that in our early experience we thought it best to avoid the excessively difficult patient until our track record could be established, and I know of four patients who we referred to Pittsburgh in our first year of operation.

Dr. Russell, regarding the bile peritonitis, it is a problem, and we have since changed our technique. Rather than performing the choledochocholedochostomy with an absorbable suture, we are now using monofilament 6-0 prolene. It is our impression that by using a nonabsorble material that the incidence of bile peritonitis is less. Again we have not critically analyzed this data. We tend to leave our T tubes in place for a minimum of 2 months.

Regarding our retransplantation rate, our overall experience was 20%. In our last 50 cases, the incidence was closer to 10%, and I believe it may be because of the multimodality immunosuppression that we are using. The more aggressive use of OKT_3, I believe, has definitely decreased our incidence of rejection.

Dr. Broelsch, I certainly agree with your concept of regionalization. Your question about convulsions, I believe I have already answered, and your question about bile peritonitis we have already discussed.

Dr. Millikan, again regarding dialysis, I believe that if we look at our series, the majority of our patients had renal failure before transplantation, and I believe that this is probably the primary cause of postoperative renal failure. We have not used peritoneal dialysis, and in only about one third of our patients who have required dialysis have we used ultrafiltration. This was used in those patients who did not have metabolic indications for dialysis but only fluid overload.

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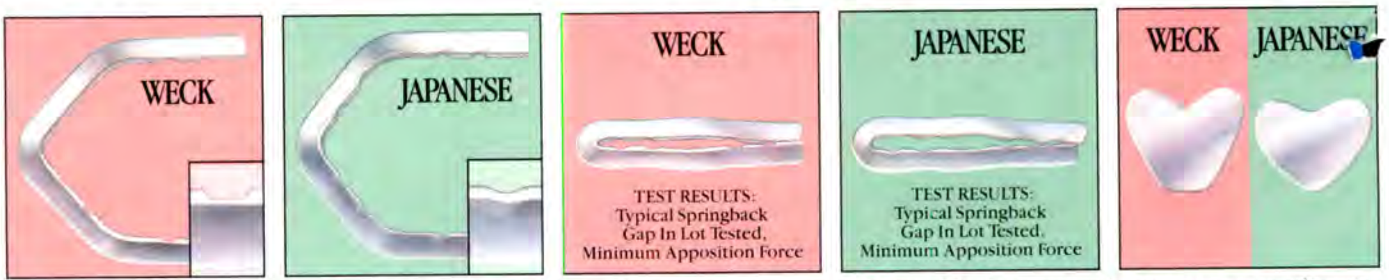

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The recently-introduced Japanese clips look the same as Hemoclip® ligating clips to the naked eye. But a recently completed independent lab study of sample quantities of clips confirms Weck's own observation of substantial differences in closure properties between the Japanese clips and Weck clips.

Vessel walls may be as thin as one-twelfth of vessel diameter.

Veins, in contrast to arteries, have very thin walls. When you consider that the vein tributaries ligated in surgery are sometimes one millimeter in diameter or smaller, with combined vessel walls as small as seven-thousandths of an inch (178 microns), according to animal studies on comparable vessels, you can appreciate the functional importance of differences in closure gap.

Arterial tributaries can be tiny, too, and although their walls are generally thicker than vein walls, arterial pressure is higher than venous pressure.

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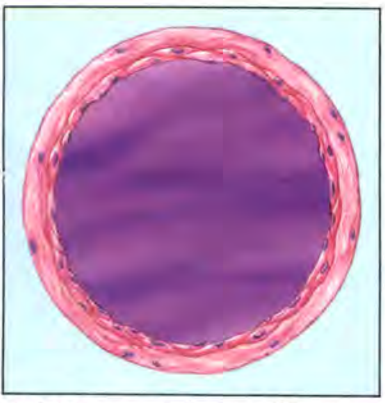
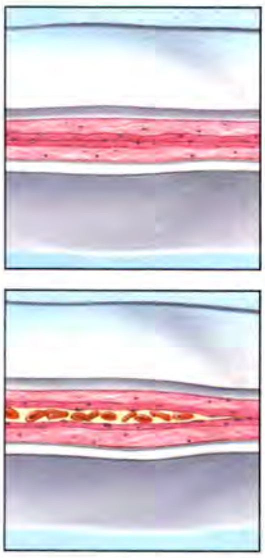




ABOVE. A vein tributary of 1mm can have a combined wall thickness of just seven-thousandths of an inch (178 microns), according to animal studies. RIGHT. A ligating clip that demonstrates greater springback than the clip you have regularly used for such vessels may be more likely to leave a closure gap larger than the vessel-wall thickness of a tiny vessel.

Weck's titanium clip vs. their titanium clip. A 23-27% difference.

Examine the chart for a visual representation of the difference in closure springback an independent research firm discovered between a set of Weck titanium medium-size clips and a set of Japanese titanium medium-size clips obtained directly from U.S. distributors of those clips. Both sets of clips were closed in Weck appliers through use of force-control devices.

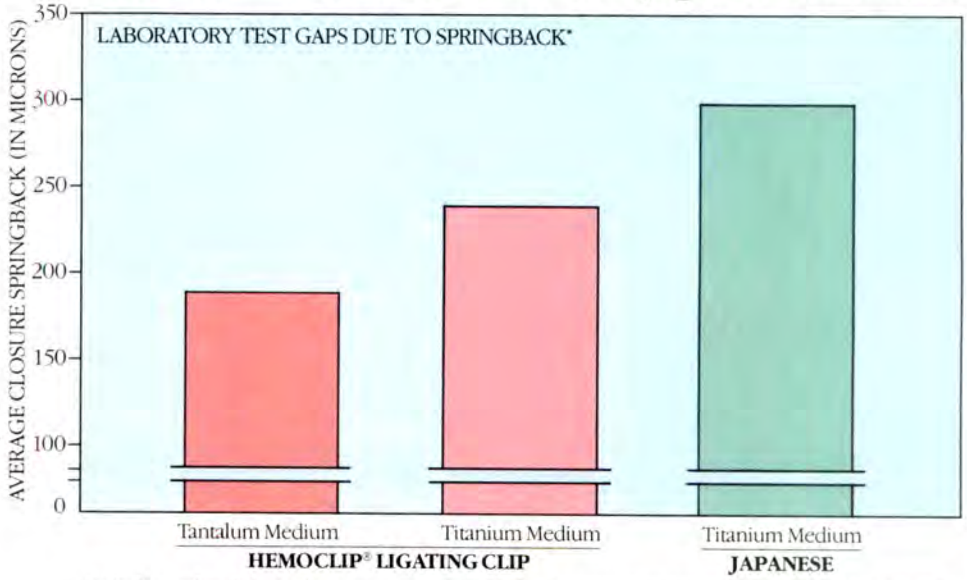
Closure of two sample sets of 25 Japanese titanium medium clips at forces adequate to achieve initial complete touching along clip legs resulted in closures of about 12 thousandths of an inch (305 microns) for the Japanese clips, 23-27% larger than the Weck titanium clip closure gap.

Weck's tantalum clips vs. their titanium clips. A 56% springback difference.

The comparison of Japanese titanium with Weck tantalum clips is even more important.

The Japanese companies make only titanium clips, and so they have sold hard on the benefits of titanium.

Tantalum is a softer material known for excellent clip closure. And the study revealed 56% and 61% larger mean closure gaps after springback for two sets of Japanese titanium clips, a ringing endorsement of the closure advantages of the Weck tantalum clips tested.



An independent lab study on two sample sets of 25 Japanese imitation clips vs. Weck clips found that the Japanese medium-size clips, closed to initial complete touching of clip legs, evidenced mean closure gaps, due to springback, 23-27% larger than Weck medium-size titanium clips, and 56-61% larger than Hemoclip® tantalum clips from Weck. Other sizes produced similar results. (Closure gap in microns-one micron = one thousandth of one millimeter).

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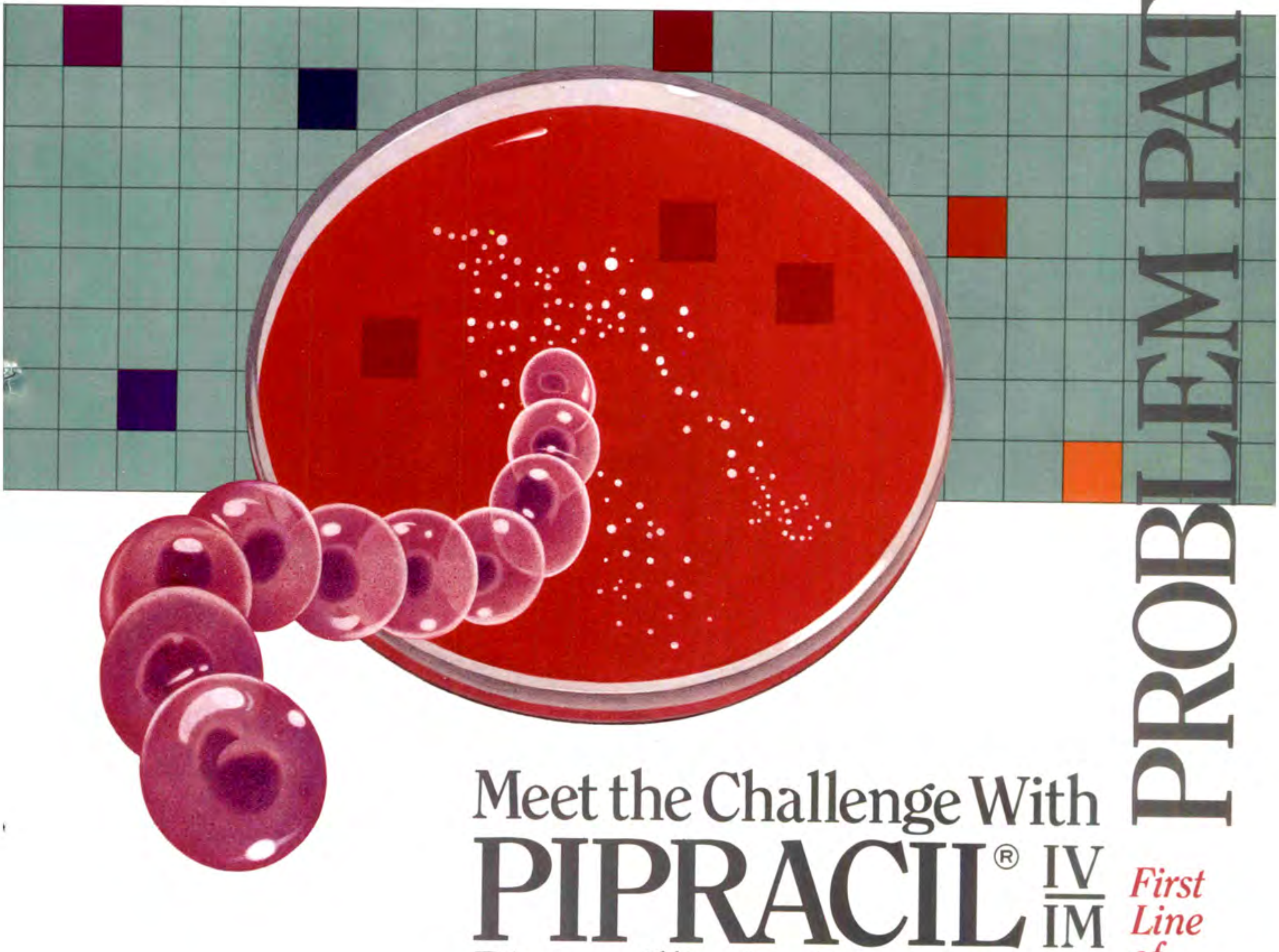

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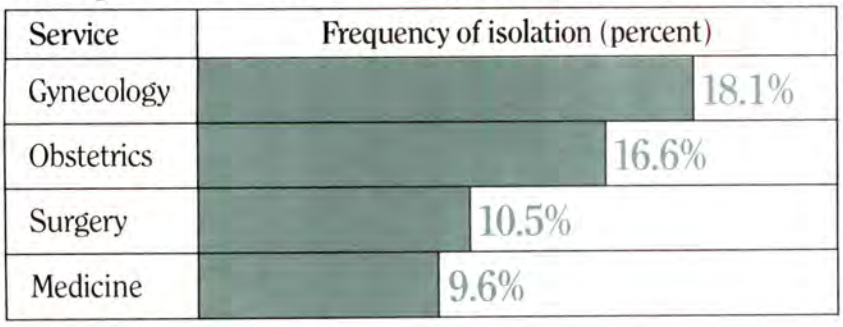

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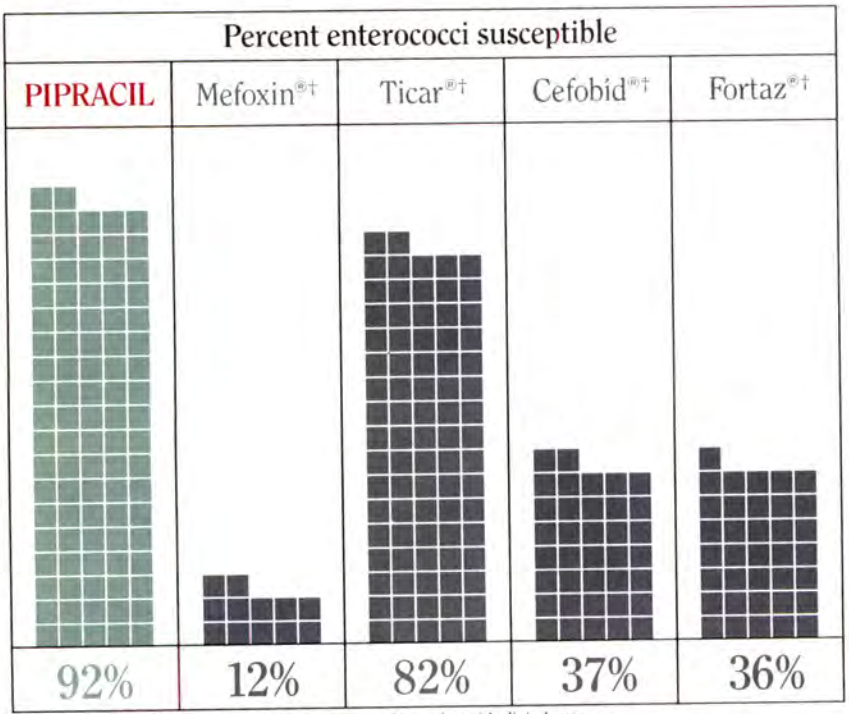

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CONTRAINDICATIONS: A history of allergic reactions to any of the penicillins and/or cephalosporins.

WARNINGS: Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients receiving therapy with penicillins. These reactions are more apt to occur in persons with a history of sensitivity to multiple allergens.

There have been reports of patients with a history of penicillin hypersensitivity who have experienced severe hypersensitivity reactions when treated with a cephalosporin. Before initiating therapy with PIPRACIL® sterile piperacillin sodium, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, and other allergens. If an allergic reaction occurs during therapy with PIPRACIL, the antibiotic should be discontinued. The usual agents (antihistamines, pressor amines, and corticosteroids) should be readily available. SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN AND INTRAVENOUS CORTICOSTEROIDS AND AIRWAY MANAGEMENT INCLUDING INTUBATION SHOULD ALSO BE ADMINISTERED AS NECESSARY.

PRECAUTIONS: General. While PIPRACIL possesses the characteristic low toxicity of the penicillin group of antibiotics, periodic assessment of organ system functions including renal, hepatic, and hematopoietic during prolonged therapy is advisable. Bleeding manifestations have occurred in some patients receiving β-lactam antibiotics including piperacillin. These reactions have sometimes been associated with abnormalities of coagulation tests such as clotting time, platelet aggregation, and prothrombin time and are more likely to occur in patients with renal failure. If bleeding manifestations occur, the antibiotic should be discontinued and appropriate therapy instituted.

The possibility of the emergence of resistant organisms which might cause superinfections should be kept in mind, particularly during prolonged treatment. If this occurs, appropriate measures should be taken.

As with other penicillins, patients may experience neuromuscular excitability or convulsions if higher than recommended doses are given intravenously.

PIPRACIL is a monosodium compound containing 1.85 milliequivalents of Na^+ per gram. This should be considered when treating patients requiring restricted salt intake. Periodic electrolyte determinations should be made in patients with low potassium reserves, and the possibility of hypokalemia should be kept in mind with patients who have potentially low potassium reserves and who are receiving cytotoxic therapy or diuretics.

Antimicrobials used in high doses for short periods to treat gonorrhea may mask or delay the symptoms of incubating syphilis. Therefore, prior to treatment, patients with gonorrhea should also be evaluated for syphilis. Specimens for darkfield examination should be obtained from patients with any suspected primary lesion and serologic tests should be performed. In all cases where concomitant syphilis is suspected, monthly serological tests should be made for a minimum of four months.

As with other semisynthetic penicillins, PIPRACIL therapy has been associated with an increased incidence of fever and rash in cystic fibrosis patients.

Drug Interactions. The mixing of PIPRACIL with an aminoglycoside *in vitro* can result in substantial inactivation of the aminoglycosides.

Pregnancy—Pregnancy Category B. Although reproduction studies in mice and rats performed at doses up to four times the human dose have shown no evidence of impaired fertility or harm to the fetus, safety of PIPRACIL use in pregnant women has not been determined by adequate and well-controlled studies. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. It has been found to cross the placenta in rats.

Nursing Mothers. Caution should be exercised when PIPRACIL is administered to nursing mothers. It is excreted in low concentrations in milk.

Pediatric Use. Dosages for children under the age of 12 have not been established. The safety of PIPRACIL in neonates is not known. In dog neonates dilated renal tubules and peritubular hyalinization occurred following administration of PIPRACIL.

ADVERSE EFFECTS: PIPRACIL is generally well tolerated. The most common adverse reactions have been local in nature, following intravenous or intramuscular injection. The following adverse reactions may occur:

Local Reactions. Thrombophlebitis (4%), pain, erythema, and/or induration at the injection site (2%) and, less frequently, ecchymosis, deep vein thrombosis, hematomas.

Gastrointestinal. Diarrhea and loose stools (2%); less frequently, vomiting, nausea, increases in liver enzymes (LDH, SGOT, SGPT), hyperbilirubinemia, cholestatic hepatitis, bloody diarrhea, and, rarely, pseudomembranous colitis.

Hypersensitivity Reactions. Anaphylactoid Reactions (see WARNINGS). Rash (1%); less frequently, pruritus, vesicular eruptions, positive Coombs tests.

Renal. Elevations of creatinine or BUN and, rarely, interstitial nephritis.

Central Nervous System. Headache, dizziness, fatigue.

Hemic and Lymphatic. Reversible leukopenia, neutropenia, thrombocytopenia, and/or eosinophilia have been reported. As with other β-lactam antibiotics, reversible leukopenia (neutropenia) is more apt to occur in patients receiving prolonged therapy at high dosages or in association with drugs known to cause this reaction.

Serum Electrolytes. Individuals with liver disease, or individuals receiving cytotoxic therapy or diuretics, were reported rarely to demonstrate a decrease in serum potassium concentrations with high doses of piperacillin.

Skeletal. Rarely, prolonged muscle relaxation.

Other. Superinfection, including candidiasis.
Hemorrhagic manifestations.

Rev. 5/86

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5-year Results of a Prospective Study of Percutaneous Transluminal Angioplasty

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This paper presents the results of a prospective study of percutaneous transluminal angioplasty (PTA) for the treatment of patients with peripheral arterial occlusive disease and identifies the variables that are predictive of long-term success. The variables believed to be important prognostically were recorded for 984 consecutive PTAs performed between July 1978 and July 1986. Success or failure was defined using a combination of clinical and objective vascular laboratory criteria. The overall long-term success was estimated by the Kaplan-Meier method and differences between curves of success rate *versus* time for each variable were determined by the Wilcoxon and log-rank statistics. The combination of variables associated with success were determined by the Cox proportional hazards regression model. For all cases, the initial success rate was 88.6 ± 1.0% and at 5 years was 48.2 ± 2.3%. The following variables, when considered individually, were associated with success ($p < 0.05$): indication for PTA, site of PTA, severity of lesion, runoff, number of sites dilated, diabetes, and the occurrence of a complication. From the Cox model, by using a stepwise multiple regression procedure, the following combination of variables were found to be predictive of success ($p < 0.05$): (1) indication (claudication *vs.* salvage), (2) site (common iliac *vs.* other), (3) severity of lesion (stenosis *vs.* occlusion), and (4) runoff (good *vs.* poor). For all combinations of these four significant variables, curves of the success rate *versus* time were calculated. In conclusion, this study has identified the combination of four variables that together predict if PTA is likely to be successful in the management of a patient with peripheral arterial occlusive disease.

PERCUTANEOUS TRANSLUMINAL DILATATION (PTA) is now accepted as an important technique in the management of patients with peripheral arterial occlusive disease. For example, during a 6-month period in 1985, in the Province of Ontario, 2257 procedures were performed for the treatment of peripheral arterial occlusive disease. PTA was carried out in 28% and surgery in 72% (Scobie TK, personal communication, 1986).

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This paper presents the 5-year results of a prospective study of PTA and identifies the variables that predict the long-term success of the procedure.

Methods

During the 8 years between July 1978 and July 1986, 984 PTAs performed at the Toronto General Hospital for the management of peripheral arterial occlusive disease were studied prospectively. The variables believed to be important prognostically were recorded and the results determined by using a combination of clinical and vascular laboratory criteria.

Patients

Patients were included in the study if they were able to return for follow-up every 6 months. The decision to perform a PTA was made in consultation between the referring physician and the vascular radiologist. The variables analyzed in this report are listed in Table 1. Details of the subcategories of the variables are listed in Table 1 or described below. If the PTA failed, the clinical grade and subsequent treatment were documented.

Radiologic Technique

Experienced vascular radiologists performed or directly supervised all procedures. The details of our tech-

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TABLE 1. *Variables and Subcategories*

1. Indication for the PTA (*i.e.*, the clinical grade)
   - Asymptomatic
   - Mild claudication (greater than 2 blocks)
   - Disabling claudication (less than 2 blocks)
   - Ischemic night pain or rest pain
   - Ulceration or gangrene
2. Site of PTA (see Table 2)
3. Severity of lesion
   - Stenosis
   - Occlusion
4. Runoff as determined from the angiogram
   - Good (for iliac PTA <50% femoral/popliteal stenosis and for femoral or popliteal PTA 2 or 3 tibial artery outflow)
   - Poor (for iliac PTA >50% femoral/popliteal stenosis and for femoral or popliteal PTA 0 or 1 tibial artery outflow)
5. Occurrence of a complication
6. Presence and severity of diabetes
7. History of previous PTA at the same site
8. Number of sites dilated
9. Specialty of the referring doctor
10. Age
11. Sex
12. Year PTA performed
13. Limb
14. Ankle/brachial systolic blood pressure ratio before PTA
15. Ankle/brachial systolic blood pressure ratio after PTA
16. Pressure gradient measured across the lesion before PTA
17. The Post-PTA pressure gradient

nique have been described previously[1] and are similar to Gruntzig's original description.[2] Aspirin, 325 mg b.i.d., and dipyridamole, 50 mg t.i.d., were administered for 1 month starting 3 days before the procedure. Heparin, 5000 units, was given at the time of the PTA.

Criteria for Success of PTA

The criteria for evaluating the outcome of a PTA have been described previously.[3] Specifically, the PTA was considered a success if the clinical grade improved by at least one level (*i.e.*, asymptomatic, mild claudication, disabling claudication, ischemic night pain or rest pain, or ulceration or gangrene) and one or more of the following vascular laboratory measurements improved: ankle/brachial systolic pressure ratio increased by at least 0.10, monophasic Doppler frequency analysis recordings became biphasic or triphasic, the Doppler pulsatility index increased by more than 20%, and/or the treadmill exercise distance at least doubled.

Data Analysis

The data were stored on a microcomputer (Hewlett Packard 9816, Hewlett Packard, Fort Collins, CO) using a database program written specifically for this study. In the following discussion, the statistical difference between groups was determined by a two tailed t-test for the continuous variables and Pearson chi square test for the discrete variables. The statistical methods for determining the long-term results are discussed in the following sections: the Kaplan-Meier method was used for univariate analysis and the Cox model was used for multivariate analysis.

Kaplan-Meier Method (product-limit method). For evaluating individual variables (univariate analysis), the Kaplan-Meier method was used to estimate the survival function, *i.e.*, the curve of the cumulative percentage success rate *versus* time of follow-up.[4] It was selected over the actuarial life table method since it gives results that are independent of the choice of the time intervals.[5] To test if there was a statistically significant difference between survival curves ($p < 0.05$), the generalized Wilcoxon (Breslow) test and the log-rank (Mantel-Cox) test were used.

Cox proportional hazards model.[6] The Cox regression model was used to: (1) determine which combination of the multiple variables are associated with success of the PTA and (2) estimate the chance of success for all combinations of the significant variables. A backward stepwise regression analysis procedure determined the significant variables ($p < 0.05$), their regression coefficients and estimated standard errors, and the likelihood ratio statistic that was used to assess the statistical significance of the variables (BMDP Statistical Package, Biomedical Computer Programs, P Series) (Statistical Software, Department of Biomathematics, UCLA, Los Angeles, CA). A microcomputer program was written to plot graphs of percentage successful *versus* time for each combination of the significant variables from the estimated regression coefficients and the estimated baseline survival function.

Results

The results will be presented in three sections: (1) description of the study population, (2) univariate analysis of the variables associated with success, and (3) multivariate analysis of the variables associated with success.

Description of Study Population

Over the 8 years between July 1978 and 1986, 984 PTAs in 902 patients were included in this study. The average age of the patients was 60.4 ± 10.2 years (mean ± 1 SD) but the patients having a femoral/popliteal PTA were an average of 4.3 years older than the aorto/iliac group ($p < 0.001$). The percentage of patients with diabetes was 19.7%, 5.1% had an abnormal blood sugar and were being treated by diet alone, 6.1% were receiving oral hypoglycemics, and 8.5% were receiving insulin. Diabetes was more frequent in the femoral/popliteal group ($p < 0.001$).

The percentage of cases referred by the vascular surgeons at our institution was 89.6%, 7.0% by cardiologists and 3.4% by general surgeons, general internists, family doctors, or others.

The indications for the procedure were mild claudication *i.e.*, more than 2-block walking distance) 5.0%, disabling claudication 79.4%, ischemic night pain or rest pain 5.1%, and ulceration or gangrene 8.0%. PTA was performed as an adjunct to a distal arterial reconstructive procedure to correct focal graft stenosis or for other indications in 2.5%. Claudication was a more common indication in the aorto/iliac group (88.4%) than in the femoral/popliteal group (79.0%) ($p < 0.001$).

The sites of PTA are detailed in Table 2. Note that 69.5% were aorto/iliac and 25.7% were femoral/popliteal. Overall, the severity of the arterial lesion was a stenosis in 80.9% and an occlusion in 19.1%; however, in the aorto/iliac segment, a stenosis was more common than in the femoral/popliteal area (87.9% *vs.* 62%, respectively, $p < 0.001$). The number of sites dilated were one in 82.8% and two or more in 17.2%. Dilatation of more than one lesion was more frequent in the aorta/iliac segment than in the femoral/popliteal segment ($p = 0.003$). The right limb was dilated in 51.5% and the left side in 48.5%. In 8.3% the PTA was repeated at the same site.

The runoff of the arterial segment just distal to the site of the PTA was normal in 50%, had less than a 50% arterial stenosis or one tibial artery occluded in 10.7%, had greater than 50% arterial stenosis or two tibial arteries occluded in 17.5%, and had a complete arterial occlusion or three tibial arteries occluded in 21.8%.

In the aorto/iliac region, the average pre-PTA pressure gradient fell from 41.8 ± 27.3 to 7.0 ± 10.9 mmHg after the PTA. In the femoral/popliteal segment, the change was from 78.1 ± 45.3 to 16.6 ± 22.4 mmHg ($p < 0.001$) but was exaggerated by catheter through the lesion.

The average pre-PTA ankle/brachial systolic blood pressure ratio was 0.58 ± 0.19 and increased to an average 0.71 ± 0.23 ($p = 0.001$).

The percentage of procedures considered technical failures because the catheter could not be passed through the stenosis was 3.8%.

Complications occurred in 9.5% of the patients as follows. Four patients (0.4%) died during their hospital stay, three died of myocardial infarction and one died of bleeding after rupture of the artery. Emergency surgery was necessary in 1.1% because of bleeding at the puncture site (1 case), severe extremity ischemia (8 cases), false aneurysm (1 case), or an arteriovenous fistula (1 case). Major complications occurred in an additional 3.4% and included shock from bleeding from the puncture site (4 cases), large hematomas delaying hospital discharge (22 cases), and ischemia not requiring emergency surgery (7 cases). Minor complications occurred in 4.6% and included small hematomas (29 cases), distal emboli without tissue damage (6 cases), arterial dissection or intimal tear that had no local consequences (3 cases), dye extravasation or intramural injection (3 cases), and other (5 cases). Complications were more common after femoral/popliteal than aorto/iliac PTA ($p = 0.02$), mainly due to the higher incidence of large hamatomas (5.1% *vs.* 2.6%, respectively).

TABLE 2. *Sites of PTA*

	N	Percent
Aortic stenosis	17	1.7
Common iliac stenosis	318	32.4
Common iliac occlusion	58	5.9
External iliac stenosis	210	21.4
External iliac occlusion	12	1.2
Common iliac stenosis and external iliac stenosis	57	5.9
Common iliac occlusion and external iliac stenosis	2	0.2
Common iliac stenosis and external iliac occlusion	3	0.3
Common iliac occlusion and external iliac occlusion	7	0.7
Common femoral stenosis	17	1.8
Common femoral occlusion	1	0.1
Profunda femoris stenosis	12	1.2
Profunda femoris occlusion	1	0.1
Femoral/popliteal stenosis above knee	131	13.4
Femoral/popliteal occlusion above knee	79	8.0
Popliteal stenosis below knee	25	2.6
Popliteal occlusion below knee	18	1.8
Tibial stenosis	1	0.1
Tibial occlusion	5	0.5
Bypass graft	9	0.9
Other	1	0.1
Total	984	100.0

After failure of PTA, 46.5% had no further treatment within 6 months, 19.8% had repeat dilatation, 25% had vascular surgery, 7.8% had amputation, and 0.9% had other treatment.

Univariate Analysis of Results

Overall results. The overall results are illustrated in Figure 1. At the time of analysis, 64.9% of the observations were censored: in 47.8% of the patients the PTA had not yet failed, 10.6% died of unrelated causes, 1% were lost to follow-up, and in 5.5% the success or failure could not be assessed because the contralateral limb was more symptomatic, another concurrent disease involved the limb, or there was development of a disease that prevented walking.

Significant variables. The Kaplan-Meier method was used to estimate the survivor function (*i.e.*, the cumulative percentage success *versus* time of follow-up) for each variable. The generalized Wilcoxon (Breslow) and the log-rank (Mantel-Cox) tests were used to determine if there was a statistically significant difference between

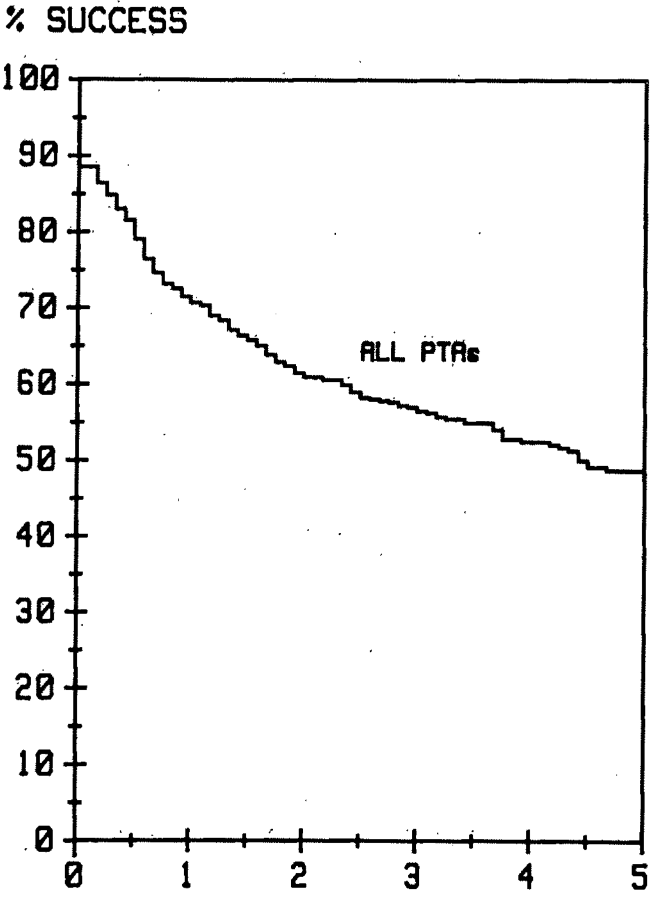


FIG. 1. Overall results for 984 PTAs.

survivor curves. The following sections describe the variables that were found to be significant by univariate analysis.

1. *Indication for PTA.* Patients having PTA because of mild or disabling intermittent claudication had a better success rate than those with limb salvage (*i.e.,* ischemic night pain, rest pain, ulceration or gangrene) as illustrated in Figure 2.

2. *Site of PTA.* As illustrated in Figure 3, the success rate of PTA of the common iliac artery was higher than other sites. Specifically, the common iliac results were superior to the external iliac (Wilcoxon = 4.1248, $p = 0.042$; log-rank = 4.682, $p = 0.030$) and to the femoral/popliteal (Wilcoxon = 14.146, $p < 0.001$; log-rank = 17.745, $p < 0.001$). Since there was no difference between the external iliac and femoral/popliteal sites (Wilcoxon = 2.940, $p = 0.09$; log-rank = 3.265, $p = 0.07$), for purposes of subsequent analyses, these sites were grouped together. By comparison to common iliac PTA, the results for this combined group of other sites were lower (Wilcoxon = 11.856, $p < 0.001$; log-rank = 14.482, $p < 0.001$).

The results of PTA of uncommon sites such as aorta, common femoral, profunda femoris, tibial, and bypass graft were not included in the overall analysis but are tabulated in Table 3.

3. *Severity of lesion.* Arterial stenoses were dilated more successfully than occlusions (Fig. 4).

4. *Runoff.* Patients with good runoff had a higher success rate than those with poor runoff (Fig. 5).

5. *Number of sites dilated.* The results were better when only one site was dilated compared with multilevel dilatations (Fig. 6).

6. *Diabetes.* Nondiabetics (defined as no diabetes or diet-controlled) had better results than diabetics controlled by oral hypoglycemics or insulin (Fig. 7).

7. *Occurrence of a complication.* If the patient did not have a complication at the time of the PTA, the long-term success rate was higher (Fig. 8).

Insignificant variables. The following section describes the variables that were not related to long-term success of PTA. The age and sex of the patient and the limb (right or left) were not significant. The results of the

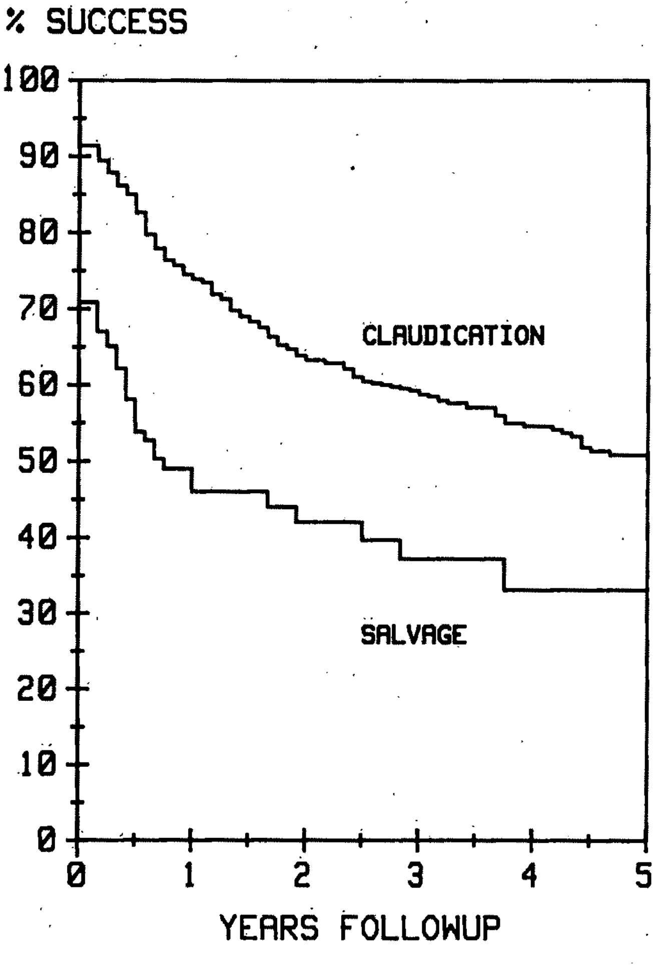
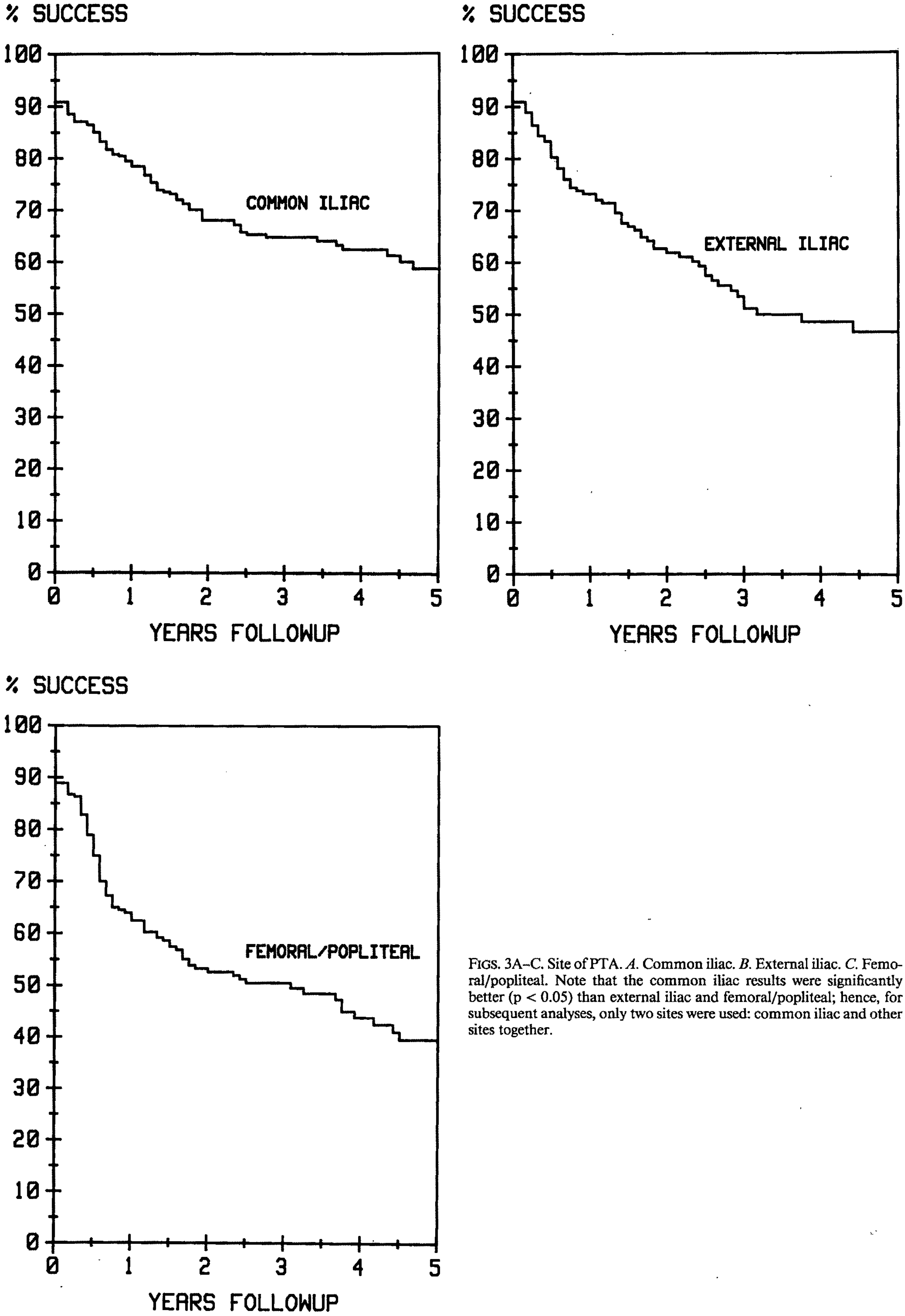


FIG. 2. Indication for PTA: claudication *versus* limb salvage. (Wilcoxon = 9.218, $p < 0.001$; log-rank = 9.590, $p < 0.001$).



Figs. 3A–C. Site of PTA. *A.* Common iliac. *B.* External iliac. *C.* Femoral/popliteal. Note that the common iliac results were significantly better ($p < 0.05$) than external iliac and femoral/popliteal; hence, for subsequent analyses, only two sites were used: common iliac and other sites together.

TABLE 3. *Results of PTA at Miscellaneous Sites*

Site	Initial No. of Patients	Success Rate			
		1 Month	1 Year	2 Years	3 Years
Aorta	17	94.1 ± 5.7	80.1 ± 10.4	80.1 ± 10.4	70.1 ± 13.0
Common femoral	18	77.9 ± 9.8	58.5 ± 12.2	48.8 ± 13.5	36.6 ± 14.6
Profunda femoris	13	46.2 ± 13.8	23.1 ± 17.7	—	—
Tibial	6	16.7 ± 15.2	—	—	—
Bypass graft	9	77.8 ± 13.9	77.8 ± 13.9	77.8 ± 13.9	51.9 ± 23.1

first 102 PTAs carried out before 1980 were not significantly different from the subsequent 882 PTAs (Wilcoxon = 5.121, $p = 0.02$; log-rank = 2.117, $p = 0.15$). The specialty of the referring doctor (vascular surgeon *vs.* other specialists) was not significant. Whether the PTA was performed for the first time or was a repeat PTA because of restenosis at the site of a previous PTA did not effect the long-term results. Neither the pre-PTA pressure gradient nor the residual post-PTA pressure gradient were related to the outcome. The ankle/brachial systolic blood pressure ratio was not a significant variable.

Multivariate Analysis of Results

As described in the following sections, the Cox regression model was used: (1) to determine which combination of the multiple variables was associated with success of the PTA and (2) to estimate the chance of success for all the combinations of the significant variables. Only iliac, femoral, and popliteal PTAs were included in this model and consequently of the original 984 cases, the number available for analysis totaled 915. If any variable had a missing value, the patient was excluded from analysis.

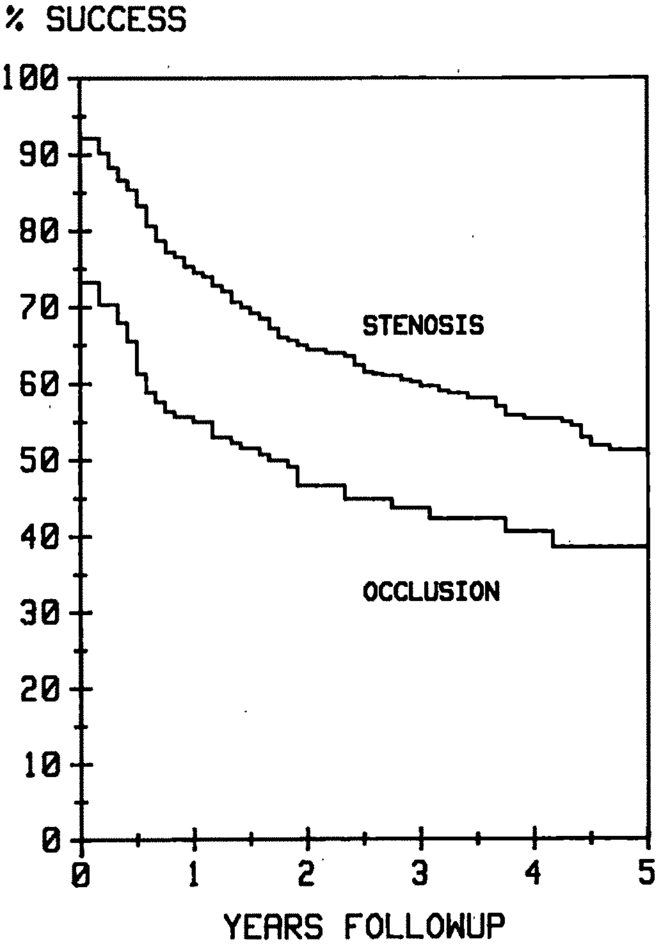


FIG. 4. Severity of lesion: stenosis *versus* occlusion. (Wilcoxon = 42.612, $p < 0.001$; log-rank = 24.459, $p < 0.001$).

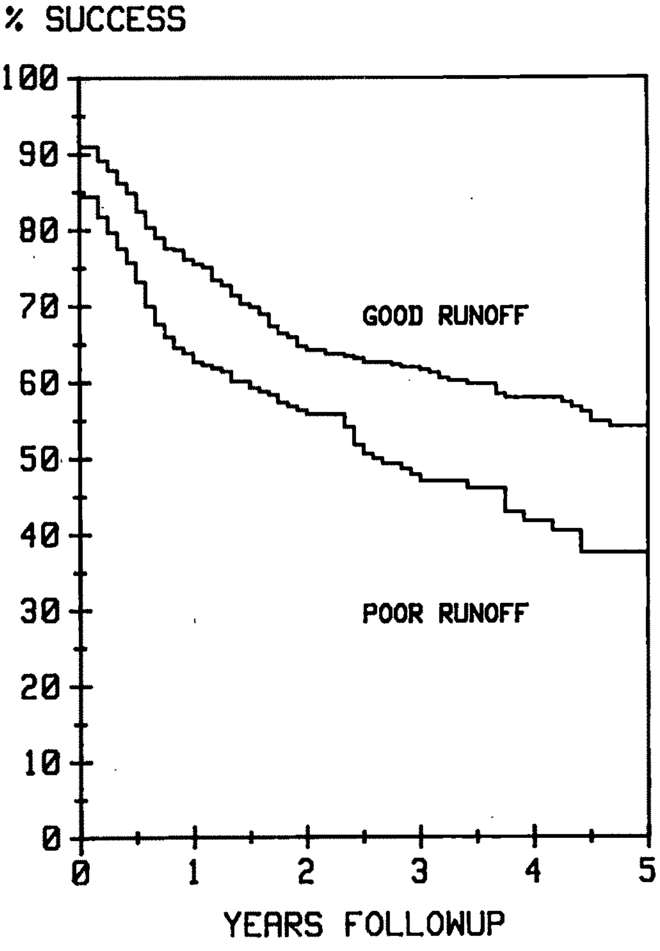


FIG. 5. Runoff: good *versus* poor. (Wilcoxon = 16.954, $p < 0.001$; log-rank = 21.923, $p < 0.001$).

Regression Analysis

A backwards stepwise regression procedure was used to identify the combination of variables that was related to success of PTA. The level of significance to enter the model was set at 0.05 to remove at 0.10. From the regression analysis, the resulting model (Table 4) was based on 870 cases with complete data and included the following combination of significant variables: (1) indication ($p = 0.0125$), (2) site ($p = 0.005$), (3) severity of lesion ($p = 0.0003$), and (4) runoff ($p = 0.0007$).

Plots of Success Rates

A microcomputer program was written to plot graphs of percentage chance of a successful PTA *versus* time for each combination of the four significant variables. At each point of time, the success rate was calculated from the estimated regression coefficients and the estimated baseline survivor function according to the following equation:

$$S(t;Z1,Z2,\ldots Zn) = S_0(t) \wedge EXP(B1*Z1 + B2*Z2 + \ldots BN*ZN)$$

where S(t;Z1,Z2,... ZN) is the success rate at time t, $S_0(t)$ is the baseline survivor function, B1,B2,... BN are the regression coefficients, and Z1,Z2, ... ZN are the coded values for the variables.

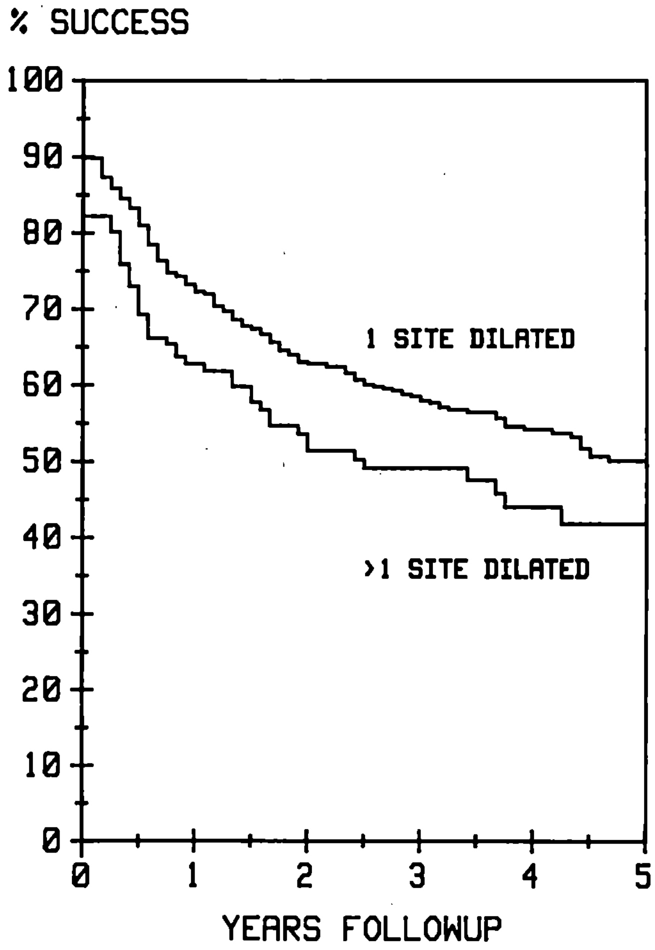


FIG. 6. Number of sites dilated: one *versus* two or more. (Wilcoxon = 9.142, p = 0.002; log-rank = 7.531, p = 0.006).

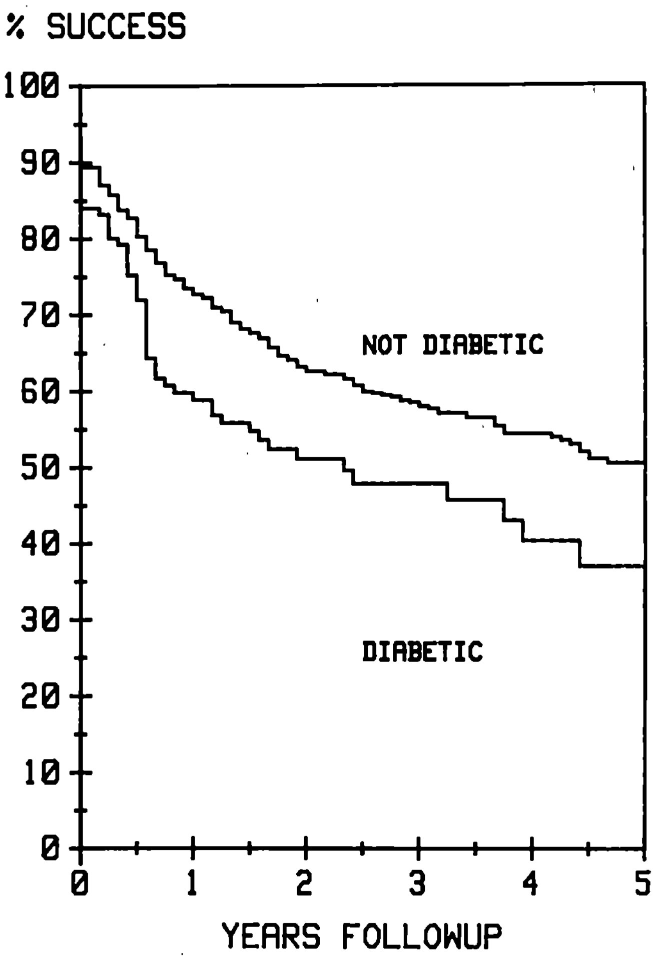


FIG. 7. Nondiabetics *versus* diabetics. (Wilcoxon = 9.348, p = 0.002; log-rank = 9.824, p = 0.002).

For the various combinations of the four significant variables, plots of the success rate *versus* time are shown in Figures 9 and 10 and the success rates are summarized in Table 5.

Discussion and Conclusions

Over the past decade, PTA has assumed an increasing role in the management of patients with peripheral arterial occlusive diseases since catheter technology has improved and the experience and competence of radiologists has increased. The low incidence of serious complications makes it an attractive alternative in the treatment of selected patients, especially if the symptoms are not disabling enough to warrant surgery or the patient is a high operative risk. However, since the over-

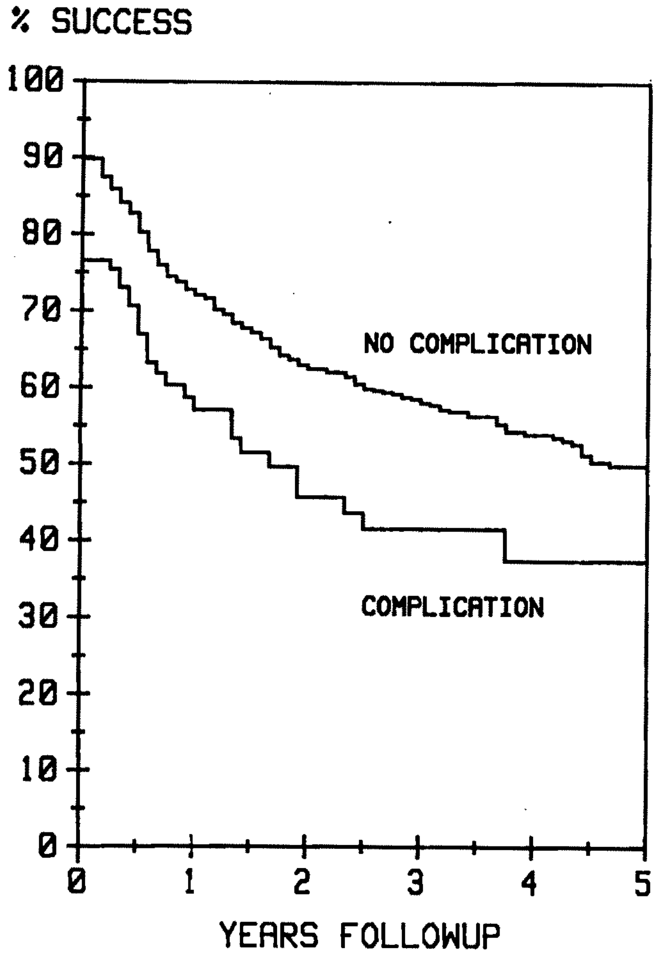


FIG. 8. No complication *versus* complication. (Wilcoxon = 13.033, p < 0.001; log-rank = 9.851, p = 0.002).

all success rate of PTA is generally believed to be lower than that reported for vascular reconstructive surgery, it is important to determine the variables that can be used to predict the long-term results of the procedure.

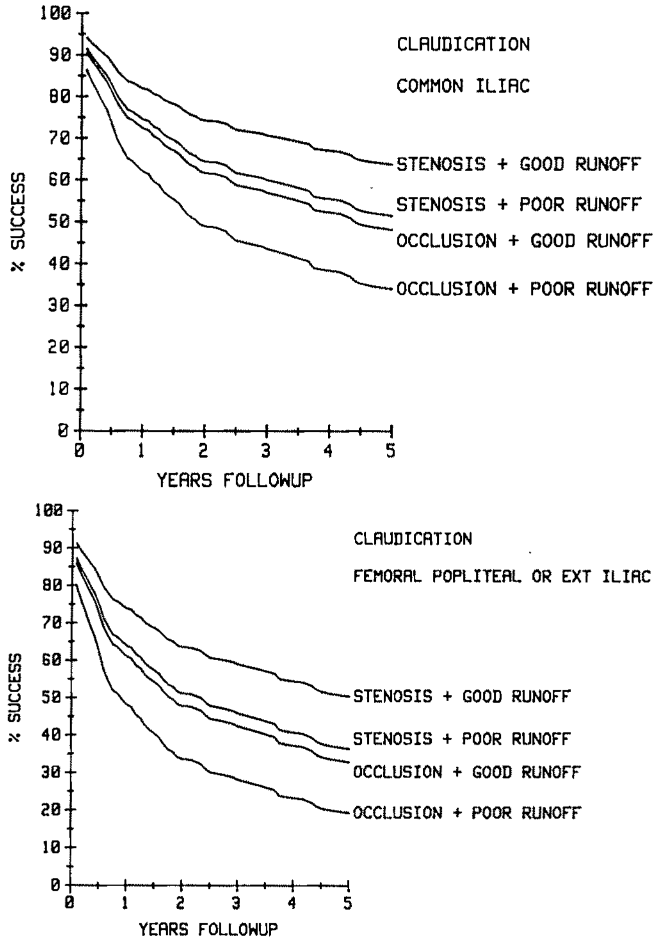


FIG. 9. Predicted results for patients with claudication and other combinations of the significant variables: site (common iliac or other), severity of lesion (stenosis or occlusion), and runoff (good or poor).

As described previously by Walden et al.,[7] the wide discrepancies in the reported results of PTA are due to differences in patient selection, criteria for evaluating

TABLE 4. *Cox Regression Model: All Cases*

Variable	Estimated Coefficient	Standard Error	Likelihood Ratio Statistic	df	p
Indication 0 = claudication 1 = salvage	0.4212	0.1619	6.24	1	0.0125
Site 0 = common iliac 1 = other*	0.3202	0.1158	7.86	1	0.005
Severity 0 = stenosis 1 = occlusion	0.4866	0.1285	13.26	1	0.0003
Runoff 0 = good 1 = poor	0.3903	0.1145	11.38	1	0.0007

* Results based on inclusion of 870 cases that met criteria for analysis and in which the data were complete (26 cases had missing data on one or more variables).

† Other = external iliac or femoral/popliteal.

the results, and methods of data analysis. In the study reported in this paper, a combination of clinical criteria and objective vascular laboratory criteria were used to determine if the procedure was a success or failure. Multiple regression techniques were used to describe the important variables that are predictive of success and to develop a model of the results.

Univariate Analysis

When the variables were analyzed one at a time, the predictors of success were found to be similar to previous reports.[8,9] The results are best when the indication for the procedure is claudication, the common iliac segment is dilated, the artery is stenosed and not occluded, the runoff is good, only one site is dilated, the patient does not have diabetes, and no complication occurred at the time of the PTA. The pressure gradient measured across the stenosis before or after the PTA was not related to outcome. In contrast to our earlier report,[10] in the model reported in this paper, we found that a repeat PTA at the same site did not have an effect on the outcome. It is important to recognize that the importance of certain variables such as smoking and length and morphologic characteristics of the lesion were not analyzed.

Multivariate Analysis

The Cox proportional hazards model was used to determine the variables that can be used to predict if a PTA is likely to be successful and to quantify the relationship between long-term success and these significant variables.[11] By using a stepwise multiple regression procedure, the combination of variables associated with

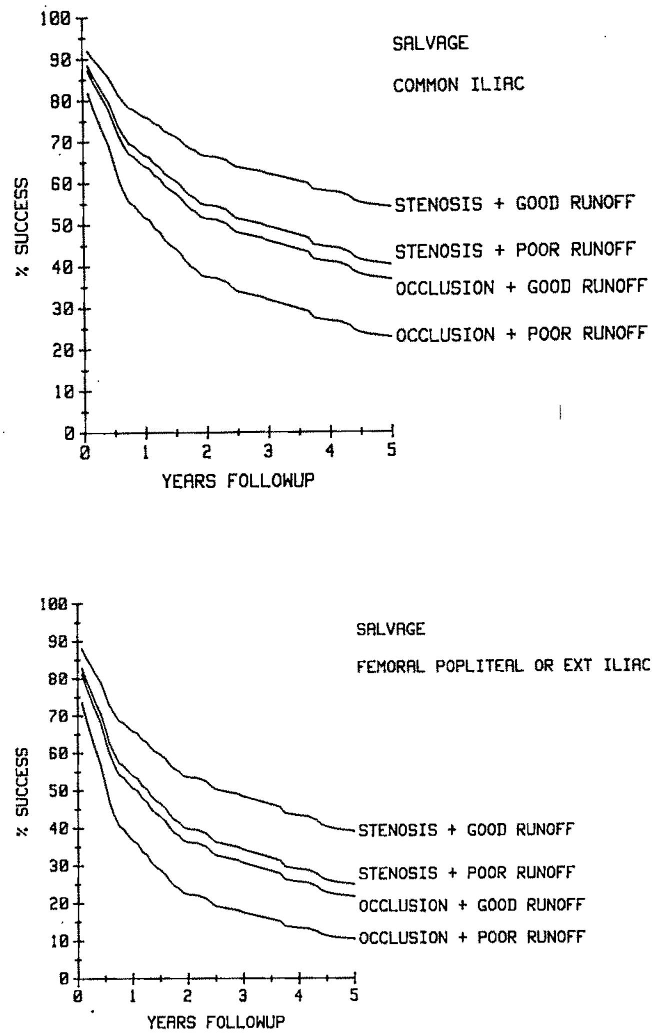


FIG. 10. Predicted results for patients having PTA for salvage.

TABLE 5. *Summary of Results of Cox Regression. Percentage Chance of a Successful PTA at 1 Month, 1 Year, 3 Years, and 5 Years Based on the Four Significant Predictive Variables*

Predictive Variables				% Success			
Indication for PTA	Site of PTA	Severity of Lesion	Runoff	1 Month	1 Year	3 Years	5 Years
Claudication	Common iliac	Stenosis	Good	94	81	70	63
			Poor	91	74	59	51
		Occlusion	Good	90	72	56	48
			Poor	86	61	43	33
	FP and external iliac	Stenosis	Good	91	75	62	53
			Poor	88	66	49	40
		Occlusion	Good	87	63	46	36
			Poor	81	51	31	22
Salvage	Common iliac	Stenosis	Good	91	73	58	50
			Poor	87	63	45	36
		Occlusion	Good	86	61	42	32
			Poor	80	48	28	19
	FP and external iliac	Stenosis	Good	88	65	48	38
			Poor	82	53	34	24
		Occlusion	Good	81	50	30	21
			Poor	73	36	17	10

FP = femoral/popliteal.

success was determined. Based on a model that incorporated the significant variables together, plots of the percentage success *versus* time have been made.

In conclusion, the risks associated with PTA are low and the chances of success can be predicted from a knowledge of four significant variables: the indication for the PTA, site of the PTA, severity of the lesion, and runoff. Thus, in deciding on the management of an individual patient, the risks and benefits of PTA can be evaluated relative to conservative management or surgery.

Acknowledgments

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DISCUSSION

DR. ROBERT B. RUTHERFORD (Denver, Colorado): Dr. Johnston and his colleagues are to be complimented on an absolutely superb, long-term analysis of a large series of PTAs performed by experts. He has given us an overall 5-year success rate of 48% and a 65% success rate in the best scenario of common iliac stenoses with good runoff done for claudication, yet currently there are three reports by radiologists in the literature of 5-year success rates for iliac PTAs ranging between 84 and 90%.

I want to point out that the difference here is simply a matter of the criteria for success. Dr. Johnston and his colleagues do *not* exclude initial failures or include redilations and, importantly, they demand both objective evidence of persisting hemodynamic benefit *and* categoric improvement.

Using similar criteria, our 5-year patency rates were 71% for iliac dilations and only 19% for femoropopliteal PTAs, but when we analyzed our data for publication at 3 years, we found that with using the differing criteria that were in the literature, we could vary the success rate on our iliac PTAs from 52% up to 86%.

In the Einover, Holland series, which reports a 90% 5-year patency for the dilation of iliac stenoses, the criteria for success were palpable femoral pulses, which the patient had before the dilation, and subjective improvement in patients who were mostly claudicators and were now 5 years older.

Clearly, we need hard data like those reported here if we are going to be able to judge the true value of PTA to our patients.

I have one question for Dr. Johnston. You previously reported that less than 10% of dilations were hemodynamically or symptomatically worse when they failed, and yet I notice a 0.4% mortality rate and a 7.8% amputation rate in this series in which 84% of the patients were claudicators.

Has this figure of less than 10% being worse off when the dilation fails held up in this larger experience that you are now reporting, and if possible, could you tell us if worsening with failure correlates with any of the variables that you have analyzed, for example, limb salvage, distal lesion, or poor runoff?

DR. JOHN J. BERGAN (Chicago, Illinois): This paper from the Toronto General Hospital is important. It is an objective summation of an experience with a treatment method that is useful to all of us who treat vascular disease, and the manuscript, as Dr. Rutherford has indicated, contains a wealth of information.

I would like to address my two remarks and single question to the rather sophisticated statistical analysis that Dr. Johnston has applied.

The number of 1000 cases gives enormous statistical power and, therefore, this study and its conclusions become a notable contribution.

Some surprisingly simple conclusions derive from his paper: one fourth of the patients in Ontario are being treated by PTA. That is certainly not our experience at Northwestern or the Chicago area. I believe that probably fewer PTA patients should be treated, certainly not those with distal occlusive disease.

Second, the complications of PTA in the study are significant. They are everywhere, even in experienced hands. They include, as has been said and I want to reemphasize, major hematomas, hemorrhage, and some of these leading to death as has been indicated by Dr. Johnston.

Similarly, in the univariant analysis, it is surprising in this study that nondiabetics fare better than diabetics because this is not true as we analyze the results of femoral distal occlusive disease operations.

It is also surprising that an early experience compared with a later experience is not different.

It is also surprising that a second dilation does not yield inferior results to the first dilation. Those are the surprising univariant results.

The multivariant analysis of 870 cases is of particular interest. Dr. Johnston is an experienced statistician. He has enormous experience, and I believe that his contribution may be of great value to us in the future because we deal with extremely complex patient problems.

Historically, vascular surgery has contributed several methods of analysis that have improved reporting in various surgical fields. I think of Harvey Butcher's contribution of introducing the life table method in analyzing patency of femoral-popliteal reconstruction.

Strandness in Seattle and Jimmy Yao, then in London, were among the first to use objective documentation of vascular reconstruction, which Dr. Johnston has employed.

I believe Dr. Johnston has given us a model, the Cox regression model, for a computer program that can make a great deal of contribution in surgery, and that is why I want to ask him a question about this.

The stepwise regression, with four variables, describes the results of his interventions. As you could see the results of his paper give support to current practice. That is, PTA is prescribed instead of surgery for common iliac stenosis in patients with claudication. Surgery instead of PTA is better for total occlusions of major arteries, especially those distal to the femoral artery.

Having said all that, Dr. Johnston, I must be critical of your study. Given the powerful statistical tool that you have developed, I am disappointed at the superficial nature of the conclusions. PTA for stenosis with good runoff is good. PTA for occlusion with no runoff is bad.

Given this tool, which, as I said, is a major contribution and may be of historic importance, therefore, how can you teach us to apply this to the next level of surgical information that we now lack?

DR. FRANK J. VEITH (New York, New York): I, too, commend Dr. Johnston for this clear, accurate analysis of angioplasty results. It is one of the few in the literature.

Based on experience with more than 600 angioplasties for limb-threatening ischemia, we continue to be enthusiastic about this treatment. Our results generally parallel those presented by Dr. Johnston.

Of importance to surgeons, we find that in most instances, angioplasty and surgery are complementary rather than competitive methods of treatment. Approximately two thirds of our patients who have angioplasty for limb-threatening ischemia ultimately require a vascular operation. One third require a complementary operation proximal or distal to their angioplasty or because the angioplasty is unsuccessful or has a complication. The other third require the operation because our successful angioplasties, like those of Dr. Johnston's group, are often palliative. That is, they often fail some time in the postangioplasty period. When these late angioplasty failures occur, patients often require a vascular operation.

Interestingly, as we showed in 1984, the downside risk of angioplasty is minimal if a appropriate close collaboration with a vascular surgeon is available. When an operation was required after an angioplasty was unsuccessful, had a complication, or failed, the operation was almost always of reasonable extent and successful.

For example, although complications that required operative correction occurred in approximately 7% of our limb salvage angioplasties, the extent of that urgent or emergent operation was usually equal to or less than the operation that would have been required if the angioplasty had not been performed.

In only 2% of all our angioplasty patients was a more extensive operation required than would have been needed without the angioplasty, and in only 0.4% of our angioplasty patients did a complication occur that precluded salvage of life and limb. It is this low downside risk that can be achieved with angioplasty that adds to its appeal, even though its benefits may not be durable and close cooperation between the angiographer and the surgeon are required to deal with problems and to achieve optimal results.

I ask Dr. Johnston if his experience with angioplasty failures and complications has been similar to ours. Were such problems almost always correctable by appropriate vascular operations?

DR. JOHN A. MANNICK (Boston, Massachusetts): I am afraid that I have nothing substantive to add to that which has already been brought up by the other discussants. However, I cannot resist one philosophical comment about this paper.

Surgeons and vascular surgeons, in particular, have recently been subjected to a barrage of criticism by medical and neurological colleagues for overly optimistic reporting of their operative results. I believe that might have been a justifiable criticism 20 years ago, but it seems to me that in this day and age it is a bum rap. It is very difficult to find in a peer review surgical journal a report of a clincal series that has not been subjected to actuarial analysis.

I believe it is ironic that invasive radiologists and interventionist cardiologists have not subjected their own work to the kind of scrutiny that surgeons are currently in the habit of doing. One sees over and over again enthusiastic endorsements of procedures from these groups based on very small numbers of patients observed for very short periods with no clear definition of what success is and no attempt at all to apply Kaplan-Meier statistics to analysis of the outcome.

I believe it is further ironic that it has taken a group of surgeons to finally evaluate adequately a large group of angioplasty patients, observed over a protracted period.

DR. K. WAYNE JOHNSTON (Closing discussion): I am honored to have had this paper reviewed in detail, and I will address the questions posed by the discussants.

Dr. Rutherford, I agree that hard end points are absolutely essential in all our studies. In peripheral vascular surgery, we have the advantage of quantitative data available from the noninvasive laboratory.

As reported previously, if the PTA fails, 10% of the patients are worse. The amputations all occurred in patients in whom prime indication for the procedure was limb salvage, and, therefore, we did not consider that they had, in fact, been worsened if the PTA failed.

Dr. Bergan mentioned a few surprising observations. Differences between our results and previous reports can likely be explained by the fact that our data were recorded prospectively and not retrospectively.

You have re-emphasized the importance of Cox regression analysis since it can correct for the confounding effect of the variables and at the same time take into account the effect of the time since the PTA.

Your criticism of the conclusions is valid. This is a descriptive, cohort study, and as such, has limitations. I agree that the causes of late failure would have been strengthened if we had examined the effects of thrombogenicity, platelet function, smoking, and other factors. Perhaps this should form the basis for future studies of patients having PTA. However, the objective of this study was to define the clinical criteria associated with success. Our results have two important applications. First, in the management of the individual patient, we now know the variables that will help us more rationally decide when PTA is indicated and to choose between conservative therapy, PTA, and surgery. Second, knowing the variables associated with a successful PTA, it should be possible to compare the results of PTA with a comparable surgical group.

Dr. Veith, our experience is quite different from yours. The majority of your patients had PTA for limb salvage, whereas 85% of our patients were claudicants. Clearly, we have corrected for this difference in our analysis; however, such observations as the consequences of failure and subsequent treatment will differ significantly. Two thirds of your patients with a failed PTA subsequently had surgery; only 25% of our failures had surgery. I agree that collaboration with the radiologist is very important.

Dr. Mannick also stressed the importance of hard end points and of the methods of statistical analysis in studies of this type.

Experimental and Clinical Results with Proximal End-to-End Duodenojejunostomy for Pathologic Duodenogastric Reflux

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Existing Roux-en-Y bile diversion procedures for duodenogastric reflux coupled with distal gastric resection or antrectomy and vagotomy have varied success due to interruption of the physiologic relationships between stomach and duodenum, the reduction of the gastric reservoir, the side effects of vagotomy, and the effect of the Roux limb on gastric emptying. A new bile diversion procedure, suprapapillary Roux-en-Y duodenojejunostomy, was studied, which eliminates the need for gastric resection to prevent jejunal ulcers by preserving duodenal inhibition of gastric acid secretion and the protective effects of duodenal secretion on the surrounding mucosa. Experimentally, the incidence of jejunal ulceration was significantly decreased by the preservation of the proximal duodenum. Clinically, bile diversion by suprapapillary Roux-en-Y duodenojejunostomy alleviates symptoms of duodenogastric reflux disease without being ulcerogenic (in the presence of normal gastric secretion) or prolonging gastric emptying.

ALKALINE REFLUX GASTRITIS is a recognized complication after operations on the stomach that distort or remove the pylorus.[1-3] It may also occur as a consequence of altered pyloric or duodenal function in patients who have not had gastric surgery.[4-6] There is evidence that the regurgitation of duodenal juice into the stomach is associated with gastric mucosal damage[7-9] and can cause symptoms of epigastric pain, nausea, and bilious vomiting.[6,10-12] Conservative therapy of the condition has been largely ineffective,[13] and in its severe form a Roux-en-Y biliary diversion procedure or a jejunal interposition is usually necessary for relief of symptoms.[2] When the former is used in patients without previous gastric resection, an antrectomy and vagotomy are required to protect against the development of jejunal ulcers. This interrupts the physiologic relationship between the stomach and duodenum, reduces the gastric reservoir, and gives rise to side effects associated with a vagotomy.[14] In addition, the Roux-en-Y limb can severely delay gastric emptying.[15,16] For these reasons, the success of a Roux-en-Y biliary diversion in improving symptoms has been only 50–80% and the incidence of jejunal ulceration has been 10–15%.[12,17-19] Consequently, a new surgical approach is needed for patients with pathologic duodenogastric reflux, especially those who have not had previous gastric surgery or whose previous surgery did not include a resection. The current study reports on the experimental development and the clinical evaluation of a new biliary diversion procedure, namely a suprapapillary Roux-en-Y duodenojejunostomy succinctly called a "duodenal switch."

Experimental Study

The purpose of this study was to determine if duodenal inhibition of gastric acid secretion and the protective effect of duodenal secretion on the surrounding mucosa could be maintained in a bile diversion procedure that preserved only the proximal duodenum in continuity with the stomach. To do so, an attempt was made to reduce the 95% incidence of jejunal ulcer formation after the Mann-Williamson preparation[20] by performing a suprapapillary duodenojejunostomy instead of a pylorojejunostomy.

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Method

Under general anesthesia, 29 adult mongrel dogs were subjected to one of four different arrangements of Roux-en-Y biliary diversion (Fig. 1). Seven dogs had an end-to-end pylorojejunostomy with an end-to-side jejunoileostomy 10 cm proximal to the ileocecal valve (classic Mann-Williamson preparation: group A). Five dogs had an end-to-end pylorojejunostomy with an end-to-side jejunojejunostomy 40 cm down the jejunum (group B). Seven dogs had an end-to-end suprapapillary duodenojejunostomy with an end-to-side jejunoileostomy 10 cm proximal to the ileocecal valve (group C). Ten dogs had an end-to-end suprapapillary duodenojejunostomy with an end-to-side jejunojejunostomy 40 cm down the jejunum (duodenal switch procedure: group D). All dogs were given the same diet and were weighed and had endoscopy at monthly intervals for up to 1 year or until death. All dogs were autopsied with inspection and removal of both surgical anastomoses. Statistical differences in the incidence of ulcer formation and degree of weight loss were determined using the Student's t-test.

Results

The incidence of ulcer formation, ulcer perforation, and degree of weight loss is shown in Figure 1. Dogs with jejunoileostomy showed profound malnutrition. When the proximal duodenum was preserved, the incidence of ulceration was dramatically reduced. The results showed that the end-to-side jejunojejunostomy was necessary to maintain nutrition, and preservation of the proximal duodenum in the acid stream was necessary to protect against ulceration. Dogs without both of these components died of either malnutrition or ulceration within 3 months.

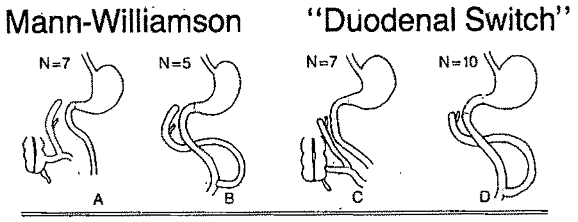
Clinical Study

The purpose of this study was to determine if biliary diversion by a suprapapillary Roux-en-Y duodenojejunostomy for pathologic duodenogastric reflux can: (1) provide symptomatic improvement; (2) heal endoscopic gastritis; (3) preserve normal gastric emptying; and (4) prevent jejunal ulceration wihtout vagotomy in patients with normal acid secretion.

Method

Patient Selection

Between January 1984 and January 1987, 202 patients were referred to the Creighton University Surgical Gastrointestinal Diagnostic and Research Unit for evaluation of foregut symptoms. Of these patients, 10 with epigastric pain, nausea, bilious vomiting, and endoscopic gastritis unresponsive to medical therapy for 2–20 years were selected for bile diversion. There were four men and six women with an age range of 28–57 years. Five patients had primary duodenogastric reflux and duodenogastric reflux developed in five patients after previous gastrointestinal surgery (Table 1). Of the three presenting complaints, epigastric pain was dominant in six of ten patients. In four patients it became worse with eating. The pain was described as burning by five patients, dull by three patients, and sharp by two patients. In six patients the pain radiated: to the chest in three, to the back in two, and to the lower abdomen in one. Nausea was the dominant symptom in two of ten patients. Nausea was associated with epigastric pain in four patients and the intake of food in two patients. Vomiting was the dominant symptom in two of ten patients, and was bilious in color in nine patients; one patient, who had a previous Nissen fundoplication, only retched. Vomiting produced relief of the epigastric pain in three patients.



	A	B	C	D
Ulcer*	86% (6/7)	100% (5/5)	29% (2/7)	10% (1/10)
Perforation	43% (3/7)	60% (3/5)	14% (1/7)	0% (0/10)
Wgt. Loss	33%	7%	33%	5%
Follow-up	3 mo.	3 mo.	3 mo.	1 year

* A vs C $p = .05$ B vs D $p \doteq .002$ A vs D $p \doteq .003$

FIG. 1. Results of four bile diversion procedures with their effect on ulcer incidence, perforation, and weight loss.

TABLE 1. *Post-surgical Duodenogastric Reflux*

Sex/Age (years)	Previous Surgery
M/57	Nissen fundoplication Redo Nissen fundoplication
M/34	Esophageal myotomy Redo esophageal myotomy and Belsey Esophagectomy, colon interposition, pyloroplasty
M/39	Truncal vagotomy and pyloroplasty Esophageal myotomy and cardioplasty
M/28	Esophageal myotomy and Belsey Pyloroplasty
F/53	Nissen fundoplication Pyloroplasty

TABLE 2. *Objective Evidence of Duodenogastric Reflux*

	Patient No.	DISIDA Scan	Alkaline pH Shift	Discriminant pH Score
Primary group	1	−	+	+
	2	+*	+	+
	3	+*	−	−
	4	−	−	+
	5	−	+	+
Postsurgical group	1	−	+	−
	2	+*	+	+
	3	+	+	+
	4	+*	+	+
	5	+	+	+

* After administration of cholecystokinin.

In each patient the symptomatic and endoscopic evidence of duodenogastric reflux was supported by one or more of three objective tests: DISIDA cholescintigraphy, alkaline pH shift on 24-hour gastric monitoring, and discriminant analysis of 24-hour gastric pH data (Table 2). Twenty healthy volunteers who were asymptomatic for gastrointestinal disease and had normal upper gastrointestinal barium studies provided a control group for the normal parameters of these tests.

DISIDA cholescintigraphy. Five μCi of Tc-99m labeled disofenin was given by intravenous injection in the fasting state. Gamma camera imaging commenced immediately and at 5-minute intervals for 60 minutes. The images acquired were stored by computer. If no duodenogastric reflux was observed during the first 60 minutes, imaging was continued for an additional 60 minutes, after which cholecystokinin was given intravenously in a dose of 0.02 μg/kg body weight over 1 minute in an attempt to provoke reflux. The timing and degree of spontaneous or provoked reflux of isotope into the stomach was noted along with abnormalities of the biliary tract and the symptoms experienced by the patient after injection of cholecystokinin. When performed on 20 control subjects, four (20%) showed evidence of duodenogastric reflux. In three controls, reflux was spontaneous and in one control it was provoked by cholecystokinin.

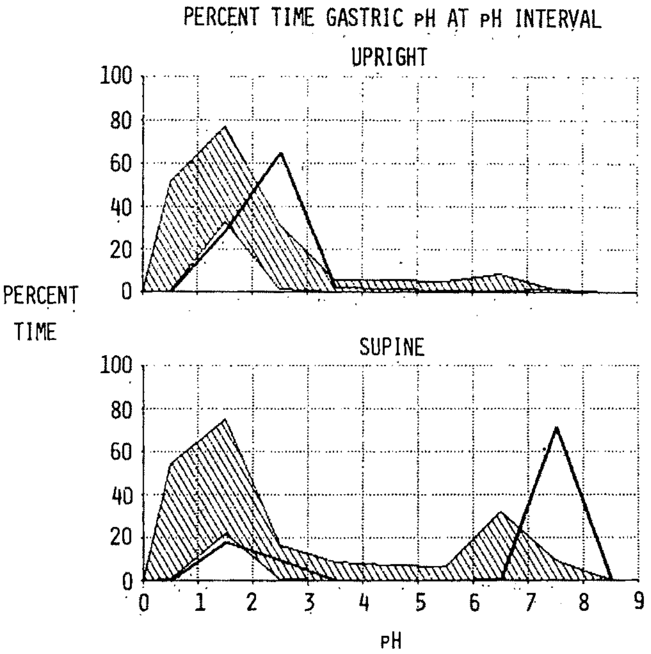


FIG. 2. Graphic display of percentage of time the gastric pH was at a whole pH interval. Control 95th and 5th percentile ranges are the shaded area. Patient data are represented by the solid line.

Twenty-four-hour pH monitoring. Outpatient monitoring of esophageal and gastric pH was performed using a computerized portable recording unit connected to combined glass probes, positioned transnasally 5 cm above and below the manometrically defined distal esophageal sphincter. The probes were calibrated in standard buffer solution at pH 7 and pH 1 before and after monitoring. The patient or volunteers were sent home and instructed to remain in the upright or sitting position until they retired for the evening, avoid strenuous exertion, and follow a diet restricted to three meals composed of food with a pH between 5 and 7. Only water was permitted between meals. A diary was kept of food and fluid intake, symptoms experienced during the monitored period, the time a supine position was assumed in preparation for sleep, and the time of rising in the morning. The patient's gastric pH data were displayed graphically as the percentage of time the pH was at a whole pH interval against a background of control data to detect an alkaline pH shift (Fig. 2). The pH data were further evaluated by a computerized discriminant analysis program developed in our unit to identify pH changes with a high probability of resulting from pathologic duodenogastric reflux. Comparison of patients with control subjects for this analysis is shown in Fig. 3.

Operative Procedure

Through an upper midline incision, the duodenum is kocherized sufficiently to allow it and the head of the pancreas to be swung freely for exposure of their posterior surfaces, and the position of the ampulla is palpated through the duodenal wall. With the thumb and index finger encircling the duodenum, it is possible to feel their close approximation at a point along the medial duodenal border just proximal to the site of the ampulla and about 2–3 cm distal to the pylorus. At this location the duodenum is dissected free of the pancreatic head by dividing the small vessels coursing between the two. This dissection is done alternately on the anterior and posterior surface taking small bites of tissue with delicate clamps. Care must be taken to avoid damage to the pancreatic portion of the common bile duct. It lies embedded just beneath the posterior surface of the pancreatic head and is identified by its linear appearance compared with the more globular adjacent pancreatic tissue. The dissection is continued until the index finger can be freely passed between the duodenum and pancreas.

At the distal end of the dissection the duodenum is divided using a GIA stapler. A pursestring suture is placed around the lateral corner of the stapled distal duodenal closure and the corner is opened. The flow of bile from this opening on compression of the liver confirms the suprapapillary transection of the duodenum. The pursestring is tied and the distal duodenal closure is oversewn (Fig. 4).

The jejunum, 25 cm distal to the ligament of Treitz, is brought through an opening in the transverse mesocolon to the right of the midcolic vessels. Its mesenteric border is freed for a distance of 2 cm and the bowel is divided between clamps (Fig. 5). Further division of the mesentery is avoided to preserve innervation.

The distal jejunal limb is anastomosed end-to-end to the proximal duodenum using an interrupted single-layer suturing technique (Fig. 6), and the proximal jejunal limb is withdrawn back through the opening in the mesocolon. This maneuver can be facilitated by initially applying the proximal jejunal clamp through the mesenteric opening before dividing the bowel. The proximal jejunal limb is anastomosed end-to-side to the distal jejunal limb 55 cm caudal to the duodenojejunal anastomosis (Fig. 7). The opening in the mesocolon is closed by suturing the margins to the circumference of the duodenojejunal anastomosis. The complete "duodenal switch" is shown in Figure 8.

This procedure was performed on the 10 patients in the study. In three patients, one of whom had a previously failed antireflux procedure, a Nissen fundoplication was added for coexisting gastroesophageal reflux disease. One patient who had gastric hypersecretion had a concomitant limited proximal gastric vegotomy to reduce acid secretion. One patient had a cholecystectomy added for cholelithiasis. Two patients had a temporary rise in their serum amylase level during the immediate postoperative recovery period. The average length of hospital stay was 13 days with a range of 9–31 days.

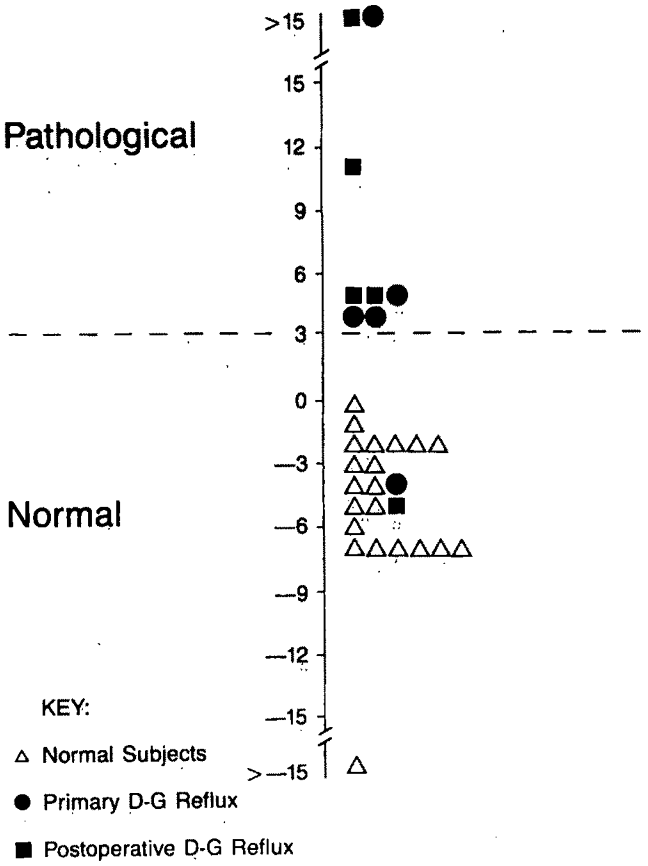


FIG. 3. Discriminant analysis of gastric pH data in duodenogastric reflux patients and controls.

Evaluation of the Operation

All patients had a preoperative and postoperative scoring of their symptoms and endoscopic evaluation of their stomach and duodenum. With few exceptions all had gastric biopsy, gastric emptying scan, gastric secretion analysis, and a serum gastrin assay before and after bile diversion. The postoperative evaluation was performed 10–33 months (median: 24 months) after operation. Student's t-test was used to determine statistical significance between preoperative and postoperative data when applicable.

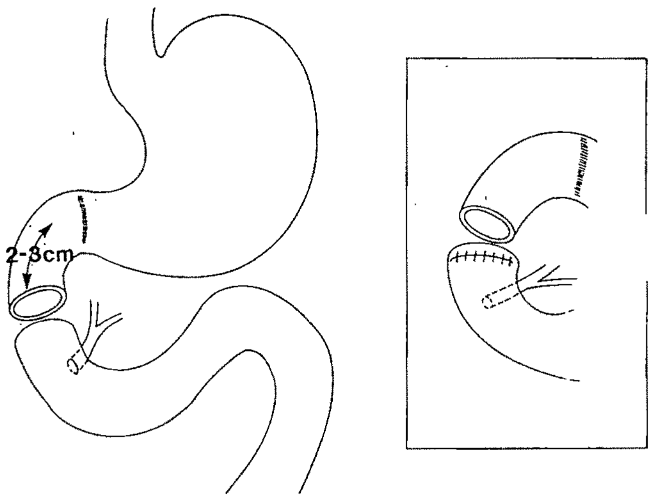


FIG. 4. Schematic diagram showing the suprapapillary transection of the duodenum 2–3 cm distal to the pylorus. Insert shows closure of the distal duodenum.

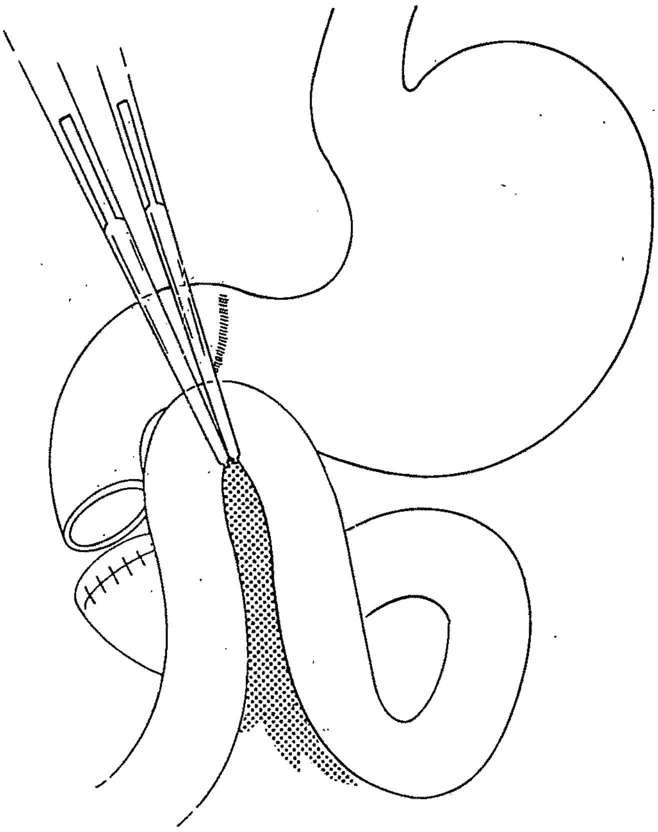


FIG. 5. Schematic diagram showing the initial construction of the Roux-en-Y in juxtaposition to the duodenum. This position is obtained by passing the loop through an opening in the mesocolon and allows construction of the Roux-en-Y without division of the mesentery.

Symptom scoring. Symptoms were scored using a detailed questionnaire completed by one of the authors. A scoring system shown in Table 3 was used to quantitate the symptoms of epigastric pain, nausea, and bilious vomiting. An overall symptom score was obtained by summing the scores for each symptom. The maximum score obtainable was 18.

Gastric biopsy. Multiple endoscopic biopsies were taken from the gastric antrum and body, fixed in formalin, and stained with hematoxylin and eosin. A scoring system was used to evaluate severity of gastritis.[21] A score of 0 to 4 was given for inflammation, 0 to 4 for corkscrew appearance of gastric tubules, and 0 to 4 for surface hyperplasia. The maximum score obtainable was 12.

Gastric emptying scan. A meal was given in the fasting state consisting of 56 g of instant oatmeal, 6 g of sugar, and 175 mL of water, mixed with 500 μCi Tc-99m sulfur colloid and followed by 240 mL of 2% milk. Caloric values of the test meal are shown in Table 4. Gamma camera counts were taken in the upright anterior and posterior projections for 40 seconds at the completion of the meal and every 15 minutes for 120 minutes. Counts per minute were adjusted to account for the decay of Tc-99m. The percentage of the initial count was plotted against time for the anterior projection, posterior projection, one-half times the sum of both projections and for a calculated geometric mean. The curve was displayed against the 95 and 5 percentile limit obtained from the 20 control subjects. In the early part of the study only the anterior projection was obtained.

Gastric analysis and serum gastrin levels. Gastric juice was aspirated using a Salem sump nasogastric tube (Sherwood Medical, St. Louis, MO) after an overnight fast. The first 15-minute sample was saved as residual basal secretion, and the following 60-minute aspirate was considered a representative basal sample. Pentagastrin was given subcutaneously in a dose of 6 μg/kg body weight and stimulated samples were obtained continuously for 15- and 60-minute periods. Hydrogen ion concentration was measured by a colorimetric titration, and the basal acid output (BAO) and maximum acid

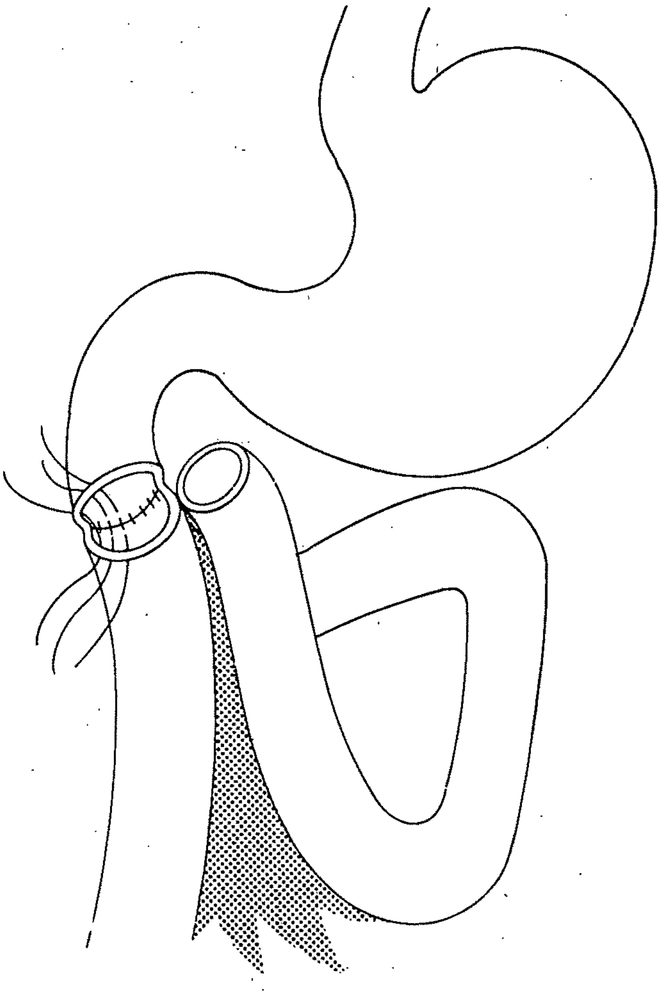


FIG. 6. Schematic diagram showing the end-to-end anastomosis of the distal jejunal limb to the duodenum.

output (MAO) in mEq/h were calculated. Hypersecretion was diagnosed when BAO was above 5 mEq/h and MAO was greater than 35 mEq/h. Fasting serum gastrin levels were measured by a radioimmune assay and recorded in picograms per milliliter.

Results

Symptoms

The preoperative and postoperative scoring of each symptom is shown in Figures 9 and 10. Bile diversion by a suprapapillary Roux-en-Y duodenojejunostomy statistically improved the overall symptom score for the five patients with primary duodenogastric reflux ($p < 0.05$), but no statistical improvement occurred in the five patients with postsurgical duodenogastric reflux. In the one patient who had persistent symptoms in the primary group, a postoperative jejunal ulcer developed that was healed completely by H2 antagonists in 6 weeks. This patient had preoperatively borderline gastric hypersecretion. In the postsurgical group, two patients had persistent symptoms. One patient had a previous colon interposition for severe reflux esophagitis after a Heller myotomy and Belsey antireflux procedure. The other patient had an esophageal myotomy and pyloroplasty for an esophageal motility disorder. Consequently, it was difficult to determine the cause of their continuing symptoms. When each patient was asked

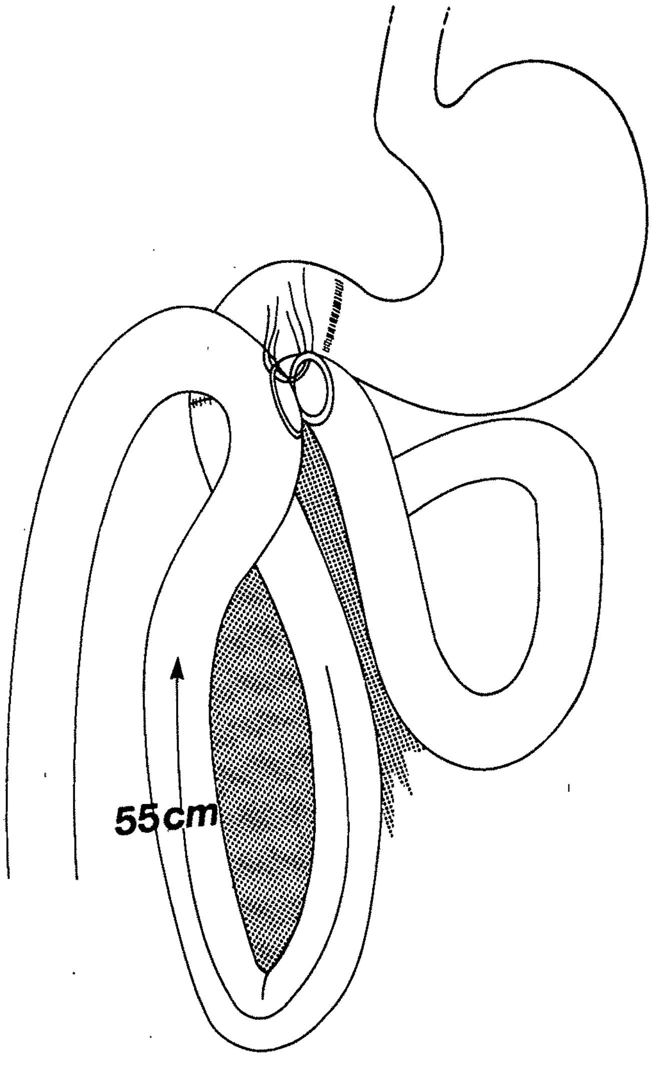


FIG. 7. Schematic diagram showing an end-to-side anastomosis of the proximal jejunal limb to the distal limb 55 cm caudal to the duodenojejunal anastomosis.

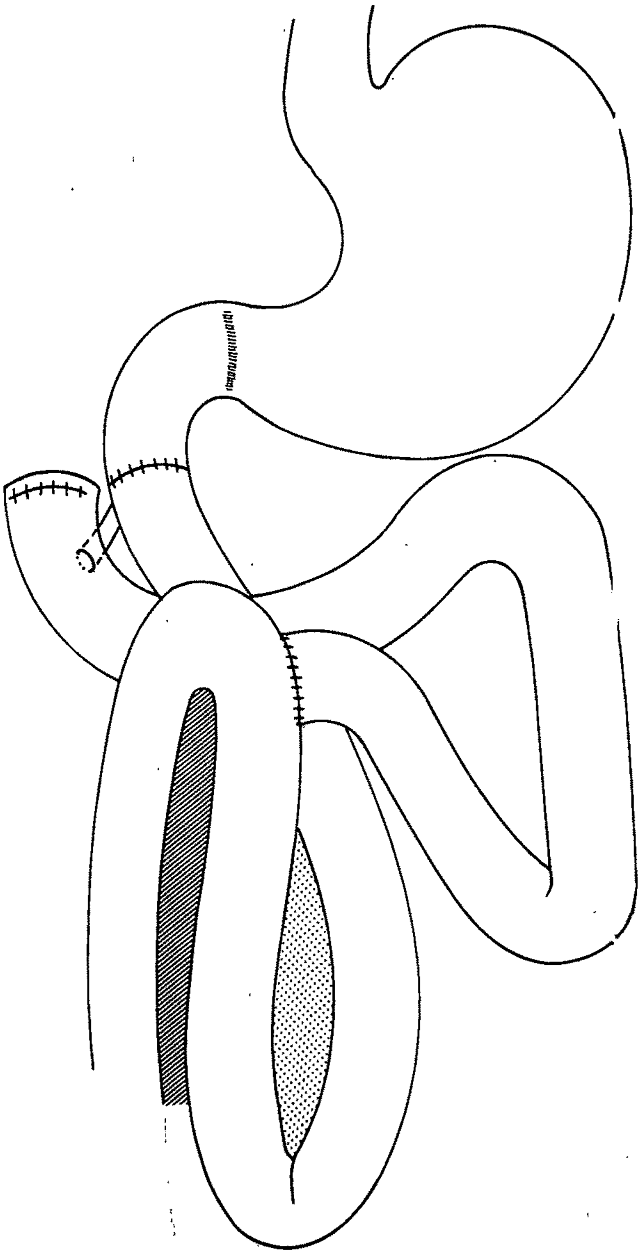


FIG. 8. Completed duodenal switch procedure used for diversion of the bile.

TABLE 3. *Scoring of Epigastric Pain, Nausea, and Biliary Vomiting*

	Score
Frequency of symptom	
Daily	4
>1 episode per week	3
>1 episode per month	2
<1 episode per month	1
Absence of symptom	0
Relationship of symptom to alimentation	
Reduced appetite or discouraged eating	1
No effect on appetite or eating	0
Severity of symptom*	
Interferes with daily activity	3
Nonrestrictive but always apparent	2
Nonrestrictive but intermittently apparent	1

* For epigastric pain only.

whether he or she would have the operation if faced with the choice again, nine of ten said yes.

Endoscopy

Table 5 shows the preoperative and postoperative endoscopic findings. Before operation, all patients had endoscopic gastritis and no evidence of esophageal or duodenal mucosal abnormalities. After operation, the endoscopic gastritis healed in all but one patient who had atrophic gastritis associated with pernicious anemia. The duodenojejunal anastomosis was normal in all patients and no bile was seen in the stomach. One of the 10 patients had a jejunal ulcer that, as mentioned earlier, healed completely with H2 antagonists in 6 weeks.

Histology

Gastric biopsy was done in six preoperative and ten postoperative patients. Histologic scores of the biopsies are shown in Table 6. Despite the improvement in endoscopic gastritis, the histologic changes persisted in five patients (score: >1), although they were only minor in three patients. The two patients with the score of seven had intestinal metaplasia that persisted over follow-up periods of 21 and 33 months. Overall, there was no statistical improvement in the postoperative histologic scores.

TABLE 4. *Caloric Values of Gastric Emptying Test Meal*

	Oatmeal	Milk	Sugar	Total
Calories (kcal)	200	12	60	380
Protein (g)	10	8		18
Carbohydrate (g)	17	11		28
Fat (g)	4	5		9

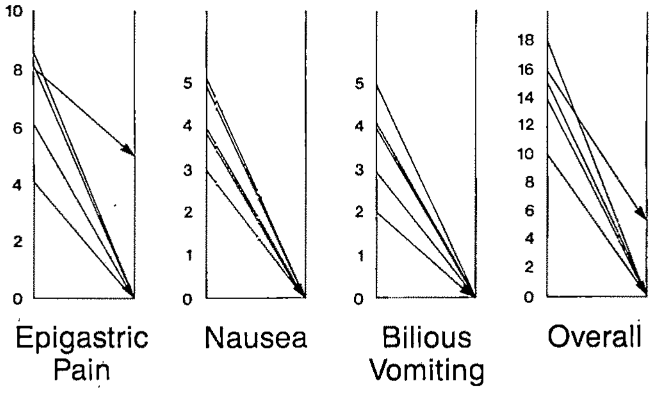


FIG. 9. Comparison of preoperative and postoperative symptoms in patients with primary duodenogastric reflux.

Gastric Emptying

Preoperative and postoperative gastric emptying curves are shown in Figure 11. All patients with primary duodenogastric reflux had normal preoperative gastric emptying. Two patients with postsurgical duodenogastric reflux had preoperatively rapid gastric emptying and in one patient the half-time was less than 15 minutes. Both patients had a previous pyloroplasty and the patient with particularly rapid emptying had a previous truncal vagotomy. With one exception, postoperative curves for both groups fell within the normal range as defined from scans on healthy volunteers and demonstrates that suprapapillary Roux-en-Y duodenojejunostomy does not retard gastric emptying. The one exception is a patient whose postoperative emptying became slightly rapid. When the postoperative geometric mean curves from seven patients were analyzed, the finding was similar.

Gastric Analysis and Serum Gastrin Levels

Table 7 shows preoperative and postoperative values for basal acid output, maximal acid output, and serum

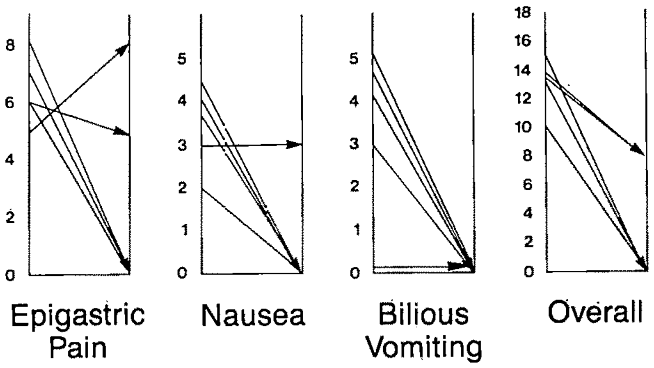


FIG. 10. Comparison of pre- and postoperative symptoms in patients with postsurgical duodenogastric reflux.

gastrin level. One patient (number 3 in the primary group) had hypersecretion before operation with elevated values for both basal and stimulated secretion. A limited proximal gastric vagotomy at the time of duodenal switch restored her acid output to within the normal range. A second patient (number 4 in the primary group) had acid secretion at the upper limit of normal range. After operation, her values crossed the upper limit and a jejunal ulcer developed that responded to H2 blockers.

Two patients with primary duodenogastric reflux had high preoperative serum gastrin levels, both of which remained elevated after operation. One patient had pernicious anemia and the other patient had normal gastric acid production and a normal secretin test.

TABLE 5. *Endoscopic Findings*

Patient No.	Primary Group	
	Before Operation	After Operation
1	No esophagitis, diffuse atrophic gastritis	No esophagitis, diffuse atrophic gastritis, anastomosis healthy, no jejunal ulcer
2	No esophagitis, antral gastritis	No esophagitis, no gastritis, anastomosis healthy, no jejunal ulcer
3	No esophagitis, antral gastritis	No esophagitis, no gastritis, anastomosis healthy, no jejunal ulcer
4	No esophagitis, antral gastritis with superficial ulceration	No esophagitis, no gastritis, anastomosis healthy, no jejunal ulcer*
5	No esophagitis, antral and body gastritis	No esophagitis, no gastritis, anastomosis healthy, no jejunal ulcer
	Postsurgical Group	
	Preoperative	Postoperative
1	No esophagitis, antral gastritis	No esophagitis, no gastritis, anastomosis healthy, no jejunal ulcer
2	Colonic interposition, antral gastritis, pyloroplasty	Colonic interposition, no gastritis, anastomosis healthy, no jejunal ulcer
3	No eosphagitis, antral gastritis,. pyloroplasty	No esophagitis, no gastritis, anastomosis healthy, no jejunal ulcer
4	No esophagitis, antral, body and fundic gastritis, pyloroplasty	No esophagitis, no gastritis, anastomosis healthy, no jejunal ulcer
5	No esophagitis, antral, body and fundic gastritis, slipped Nissen, pyloroplasty	No esophagitis, no gastritis, anastomosis healthy, no jejunal ulcer

* A postoperative jejunal ulcer developed 1 year after surgery. The ulcer healed on H2 blockers without complication.

TABLE 6. *Histologic Score for Alkaline Reflux Gastritis**

Patient No.	Before Operation	After Operation
	Primary Group	
1	—	7
2	5	7
3	5	1
4	—	0
5	1	3
	Postsurgical Group	
1	1	1
2	—	1
3	—	3
4	8	0
5	4	3

* Scale of 0 to 12.

Body Weight

There was no statistically significant change in body weight after surgery.

Discussion

Suprapapillary Roux-en-Y duodenojejunostomy was designed to provide diversion of bile and pancreatic juice while leaving the proximal duodenum, pylorus, and stomach undisturbed. Conceptually, this has benefits over the classical Roux-en-Y gastrojejunostomy diversion procedure: it allows preservation of a normal gastric reservoir, antral and pyloric function, duodenal inhibition of acid secretion, and stimulation of the duodenal mucosa by chyme. An important part of the latter is the release of gastrointestinal hormones and digestive gland secretion. These functions are lost after the classical operation and result in early satiety, delayed gastric emptying, dumping, and the occurrence of jejunal ulcers. The latter has been reported to be as high as 10–15%. The incidence of ulcers can be reduced by the addition of vagotomy,[18] but this is not without its own side effects. Even with vagotomy, the possibility of jejunal ulceration still exists.[17]

The fear of performing a proximal duodenojejunostomy is the possibility of a high incidence of jejunal ulcers since the jejunum is exposed to the full barrage of gastric acidity without neutralization by biliary and pancreatic secretions. This fear may be unwarranted because of two physiologic factors. First is the observation that instillation of acid into the proximal duodenum suppresses basal and stimulated gastric acid secretions This effect was first shown in dogs by Sokalov[22] and widely confirmed by others.[23–29] The same mechanism

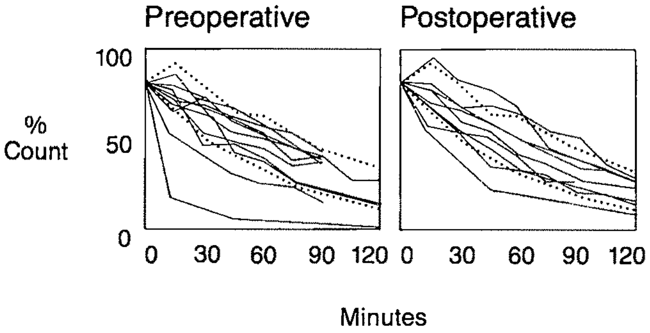


FIG. 11. Comparison of preoperative and postoperative gastric emptying scans taken in the anterior projection in patients who have undergone a duodenal switch procedure. The dotted line represents the 95th and 5th percentile limits measured in control subjects.

was shown in humans by Griffiths[30] and Shay et al.[31] Second is the observation in animals[32] and humans[33] that the proximal duodenum secretes bicarbonate, which, along with the overlying layer of mucus, provides a barrier to protect the surrounding mucosa from acid and peptic damage.

The current study indicates that these factors remain operational when the proximal duodenum is preserved in continuity with the stomach after diversion of biliary and pancreatic secretions. In the animal studies, there was a significant reduction in the incidence of jejunal ulceration compared with that observed with a direct pylorojejunostomy. In the human studies, jejunal ulceration did not occur unless gastric hypersecretion was present.

The advantage of a suprapapillary Roux-en-Y duodenojejunostomy is that a vagotomy and alteration of gastric or pyloric anatomy are not necessary to prevent jejunal ulceration. This allows preservation of normal gastric function and avoids the complications associated with vagotomy and resection.[12,34,35] Critchlow et al. reported an experience with a similar procedure in three patients for the treatment of symptomatic duodenal diverticula.[36] No jejunal ulceration occurred and the patients remained symptom free on subsequent follow-up. An important observation is that patients do not have delayed gastric emptying after a "duodenal switch" as reported after a Roux-en-Y gastrojejunostomy and vagotomy. Consequently, this delay must be due to either the vagotomy or denervation of the Roux limb. For this reason, we avoid dividing the mesentery to preserve the nerve supply to the jejunum when constructing the Roux-en-Y.

The endoscopic gastritis observed in patients with duodenogastric reflux is believed to be due to regurgitated bile and pancreatic enzymes. Both have been shown experimentally to be capable of damaging the gastric mucosa in animals,[37,38] and in humans, the presence of both in the stomach has been associated with gastric ulcer.[39,40] The "duodenal switch" procedure effectively diverted bile and pancreatic secretion and resulted in endoscopic healing of gastritis.

The histologic gastritis observed before operation rarely resolved. Persistence of intestinal metaplasia after bile diversion appears to account for elevated postoperative histologic scores. This phenomenon may be analogous to the development of Barrett's epithelium with gastroesophageal reflux and, like Barrett's, a return of the mucosa to normal histology, after removal of the stimulus to its production, may never occur or may take many years.

In humans, duodenogastric reflux occurs sporadically.[41] Increased duodenogastric reflux has been measured in patients with esophagitis, gastric ulcer, cholelithiasis, and previous cholecystectomy.[6,9,42–44] We reported five patients with the primary abnormality discovered during an evaluation of foregut symptoms. All complained of epigastric pain, nausea, and bilious vomiting. Two patients had documented gastroesophageal reflux disease, none had cholelithiasis, but all had endoscopic gastritis. Four of these patients had an alkaline gastric pH shift when measured over 24 hours.

TABLE 7. *Basal and Stimulated Gastric Secretion Analysis (mEq/h)*

	Patient No.	Preoperative		Postoperative		Serum Gastrin (pg/mL)	
		BAO	MAO	BAO	MAO		
Primary group	1	0	0	0	0	>1000	>1000
	2	2.1	17.4	1.0	9.8	55	43
	3	12.5	42.3	2.0	16.6	35	44
	4	4.7	29.0	5.0	39.0	—	15
	5	1.0	33.7	0.7	35.0	443	378
Postsurgical group	1	3.0	17.8	—	—	—	—
	2	—	—	3.8	9.3	—	60
	3	—	—	1.6	2.0	—	20
	4	1.5	25.1	0.6	4.4	46	39
	5	1.5	4.5	0.4	6.8	—	50

When subjected to a discriminant analysis, the alkaline change had a high probability of being caused by excessive duodenogastric reflux. One patient, with gastric hypersecretion, did not show an alkaline shift or a positive discriminant analysis, but duodenogastric reflux was confirmed by radionuclide scanning. It may be that patients who have duodenogastric reflux after an acid-reducing procedure, initially had the primary disease, which was masked by hypersecretion. A clue that duodenogastric reflux might be present in a patient with hypersecretion is the persistance of bile reflux symptoms while the patient is receiving H2 blockers. Such patients are likely to have persistence of symptoms after vagotomy, and the addition of a duodenal switch to the initial procedure may be, as in our patient, beneficial to the successful control of symptoms.

The mechanism by which reflux occurs in the patient who is not operated on is poorly understood but probably related to a functional abnormality of the duodenum or pylorus.[5,41] The abnormality does not appear to affect gastric emptying in that all our patients who did not have previous surgery showed normal emptying curves.

Lawson showed in animals that severe duodenogastric reflux can cause a reduction in the number of parietal and chief cells in the gastric fundus.[38] In humans, a decrease in acid production has been observed with duodenogastric reflux and was ascribed to the loss of parietal cells or back diffusion of hydrogen ions. In severe forms, this can cause alkalinization of the antrum and elevated serum gastrin levels. Two of our patients with primary disease had a high serum gastrin level, one of whom had pernicious anemia. It may be that pernicious anemia is the end stage of duodenogastric reflux.

Of the five patients with postsurgical duodenogastric reflux, two had persistent epigastric pain and nausea after the biliary diversion procedure. Both patients had a history of esophageal motility disorder requiring a myotomy for relief of dysphagia, and one patient had an esophagectomy and colon interposition for intractable symptoms. This history may account for some of their current complaints.

In two patients with primary disease, a concomitant Nissen fundoplication was done to correct coexisting documented gastroesophageal reflux. All patients with postsurgical disease had a prior esophageal procedure: three had esophageal myotomy, and two had an antireflux operation. Thus the overall incidence of esophageal disease in our patients with duodenogastric reflux was 70% (7 of 10), suggesting that an underlying diffuse foregut disorder exists. Initially, the symptoms of duodenogastric reflux, gastroesophageal reflux, or an esophageal motor disorder may predominate. Correction of the predominant component may allow the symptoms of the other components, if present, to emerge. This emphasizes the importance of a careful preoperative and postoperative evaluation of patients with benign foregut disease. What might be considered a failure of a previous procedure to improve symptoms is, in reality, the emergence of symptoms due to another abnormality not appreciated before the operation.

Prolonged medical therapy consisting of H2 antagonists, antacids, and sucralfate did not relieve symptoms of epigastric pain, nausea, and bilious vomiting, and was the driving force for surgical therapy. Our experience indicates that if the patient has preoperatively marginal or definite hypersecretion, a limited proximal gastric vagotomy should be performed with the initial operation. Patients with normal and low gastric acid secretion do not need a vagotomy to remain free from jejunal ulceration.

In summary, bile diversion by "duodenal switch" preserves the suprapapillary duodenum. Experimentally, this causes a significant decrease in the incidence of jejunal ulceration. Clinically, the operation corrects pathologic duodenogastric reflux, alleviates the symptoms of the primary disease, improves the symptoms of the postsurgical disease, heals endoscopic gastritis, does not delay gastric emptying, and is, in the presence of normal acid secretion, not ulcerogenic.

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DISCUSSION

DR. JOHN L. SAWYERS (Nashville, Tennessee): In 1965, Toye and Williams in the United Kingdom described a new postgastrectomy syndrome, which was reflux gastritis, and differentiated this from chronic afferent loop syndrome, which had been confused with alkaline gastritis. They treated this "new syndrome" by inserting an isoperistaltic jejunal segment between the gastric pouch and the duodenum. In 1974, Dr. Herrington and I presented at the American Surgical Association results of an isoperistaltic jejunal segment *versus* Roux-en-Y gastrojejunostomy for alkaline reflux gastritis and concluded that the latter was superior.

We currently have 110 patients followed from a minimum of 1 to more than 10 years with a Visick I or II clinical grading, *i.e.*, a satisfactory clinical result, in 79% of the patients. The 21% of patients with less than a satisfactory result have no evidence of bile reflux gastritis into their stomach, but they have motility problems of slow gastric emptying or Roux limb syndrome. In two of the 110 patients, a marginal ulcer developed despite what we believed was a complete truncal vagotomy.

Is Dr. DeMeester's new operation of a duodenal switch an improvement over Roux-en-Y gastrojejunostomy? There are a few things that bother me about the technique, and I wish he would elaborate to us how he locates the exact point in the second part of the duodenum where he puts his GI stapler and avoids injury to the distal end of the common bile duct and accurately locates the ampulla. It is my impression from reading the manuscript that the duodenum is not open to locate the ampulla.

Gastric emptying was almost normal in all of his 10 patients. This is contrary to results that we have seen, and others have reported, after pyloric sparing pancreaticoduodenectomy operations in which about one third of the patients have delayed gastric emptying, at least for a while.

Dr. DeMeester, is this difference due to sparing the duodenal pacemaker because you divide the duodenum more distally in your duodenal switch operation?

Five of his patients who had remedial operation had no previous gastric operation. I have never done a remedial operation on anyone for primary duodenogastric reflux. I am concerned that there is an increasing number of patients diagnosed as having reflux gastritis with insufficient evidence to substantiate the diagnosis. Concern exists that some surgeons may be too eager to do remedial operations on patients with reflux gastritis.

Dr. DeMeester, however, has carefully studied his patients to document reflux, and I am sure that they all were symptomatic.

Although I am enthusiastic about operations to spare the pylorus, I am concerned about postoperative jejunal ulcer developing after this procedure. One of his ten patients has already had a jejunal ulcer, and I would like to ask him why he does not add proximal gastric vagotomy to all these patients since it is a safe type of vagotomy with minimal side effects.

DR. WILLIAM SILEN (Boston, Massachusetts): My colleague, Dr. Jonathan Critchlow, and I about 1 year ago described an identical procedure in the *Annals of Surgery*, but using that procedure for a different purpose. We have now used this same procedure in five patients who had recurrent cholangitis and pancreatitis associated with the accumulation of food and debris in a juxtapapillary duodenal diverticulum, with excellent results in all cases. Peptic ulceration has not developed in any patient, and although two of them have had early transient delay in gastric emptying, the long-term results have shown no problems with gastric emptying in patients followed for up to 5 years.

I recommend this procedure to avoid a difficult and potentially hazardous dissection of a duodenal diverticulum if one needs to come to grips with that problem. For the indication I am describing, the defunctionalized limb includes the second, third, and fourth parts of the duodenum, and therefore the jejunum can be transected about 20 cm distal to the ligament of Treitz, but the end-to-side jejunal jejunostomy can be made very close to the end-to-end duodenal jejunostomy, thus allowing adequate mixing of food with bile and pancreatic juice, which in our opinion is the most important factor in preventing peptic ulceration.

There are abundant data in the literature that indicate that if one interferes with adequate fat digestion by whatever means, that is diversion of bile and pancreatic juice *far* distally in the small intestine by ligation of the pancreatic duct or by extensive resection of the small intestine, the well-known inhibitory effects of adequately digested and micellerized fat in the small intestine are lost. In the procedure that we have described to divert gastric content away from the diverticulum, mixing and fat digestion can proceed virtually normally because the end-to-side jejunostomy can be placed close to the end-to-end jejunostomy.

Whether the more distal displacement of bile and pancreatic juice for diversion of duodenal content away from the stomach, as required for the indications proposed by Dr. DeMeester and his colleagues, will eliminate the well-known enterogastrone inhibitory effects of fat, remains to be seen. It is going to depend on whether 55 cm is enough to interfere with adequate fat digestion and inhibition of acid secretion by micellerized and digested fat.

Finally, I believe, as alluded to by Dr. Sawyers, one must exercise great caution in the diagnosis of pathologic duodenal gastric reflux because the criteria for this entity are far from precise.

DR. C. THOMAS BOMBECK, III (Chicago, Illinois): I, too, was privileged to read this manuscript last night and would commend it to all of your attention. It is an excellent review of what is a very difficult and fortunately uncommon subject. The information in this paper could well be measured by the pound rather than by the page.

There are two outstanding or somewhat remarkable findings in this paper, and the first of them is the construction of a Roux loop drainage procedure that essentially has no component of the Roux Loop syndrome. That is, 100% incidence of a perfectly functioning Roux loop drainage procedure.

The authors attribute that to preservation of the innervation of that Roux loop, although it is placed somewhat down the duodenum. There are many other explanations for that, and I wonder if they have pursued any of them, for instance, measuring duodenal hormone levels with various stimuli in both the patients and in the animals.

The second remarkable finding is the incidence of improvement in bile gastritis. As all of you know, and has already been mentioned two or three times, the selection criteria for patients with bile gastritis for eventual surgical treatment are not at all clear. Many people have attempted to use the identity of the refluxed material: what composes it, how much bile salt there is present, how much trypsin, and so forth. There has not been any adequate explanation for this.

The authors use two methods of selection of these patients. In the first they say that they simply selected 10 of 202 patients from this patient population. I wonder what criteria they used to do that with.

Secondly, they investigated all these patients using one relatively new modality, which was the alkaline shift method using 24-hour intragastric pH measurements. That is relatively unusual and may account for their high incidence of success. I wonder what they do attribute that to.

Finally, I would echo everyone's concern about the omission of vagotomy in this group of patients. Both in the human and in the dog series, I notice now, the incidence of jejunal ulceration was 10%. The addition of a limited highly selective vagotomy to this group of patients would require no more than about 30 minutes more in the operation with essentially no complications, and it would seem to me to be a worthwhile thing to do, at least until many more patients are accumulated.

DR. EDWARD WOODWARD (Gainesville, Florida): The Roux-en-Y syndrome of delayed gastric emptying is certainly not either well understood or completely solved. Most of the patients we see with alkaline reflux gastritis have had a truncal vagotomy and a Billroth II antrectomy. If one transects the afferent limb and implants it 60 cm down the efferent jejunum, only one fourth of such patients will have a satisfactory result. Another one fourth will be completely disabled by severe delay in emptying of the gastric remnant. We have found that those patients who will tolerate Roux-en-Y duodenal diversion can be delineated by a measurement of solid phase gastric emptying. We use technetium-99 incorporated in a poached egg. If 50% of the isotope has emptied from the stomach in the first 30 minutes, the patient will tolerate the operation outlined above. In those patients with delayed solid phase emptying, we have used extensive subtotal gastrectomy with the Roux-en-Y procedure. Although the results seem to be somewhat better, they are certainly not uniformly so. In about three fourths of such patients, the Roux-Y limb of jejunum is itself involved in delayed transit.

The authors have demonstrated both in the experimental animal and in humans that preserving the first portion of the duodenum in continuity will minimize marginal ulcer formation, presumably by inhibiting gastric acid secretion. They are to be congratulated on these excellent observations, and the operation they present for use in patients would certainly preclude the necessity for truncal vagotomy to avoid marginal ulcer. The 10% incidence of ulceration they observed, however, would seem that parietal cell vagotomy would be needed. However, it seems there would be a limited patient population in whom the procedure could be used. The authors have found five patients with primary reflux alkaline gastritis in the presence of an intact stomach and intact vagal innervation. I find this surprising indeed since we have seen only three such patients in 20 years.

DR. TOM R. DEMEESTER (Closing discussion): I would like to thank the discussants for their comments and thought-provoking questions.

First I will answer Dr. Sawyers' question about locating the papilla. After kocherization, the papilla can often be palpated through the wall of the duodenum between the forefinger and thumb, the former on the posterior and the latter on the anterior duodenal wall. In addition, a point can be localized along the medial border of the duodenum where the thumb and forefinger approximate each other. A 1-cm hole between the medial border of the duodenum and the pancreas can be made at this point by careful dissection using small clamps. Initially, we used to open the duodenum and press on the liver to encourage bile flow to assure ourselves that we were proximal to the papilla. Now that we have gained confidence, we use the GIA stapler to divide the duodenum, opening only the proximal staple line to make the anastomosis.

Dr. Bombeck and Dr. Sawyers both asked about delayed gastric emptying and why it did not occur in our patients. There are at least three possible answers to this question and probably many more opinions, since this is currently an area of intense interest.

First, five of our patients had a normal anatomical stomach and pylorus and five had a previous pyloroplasty. None had a gastric resection, and that may play a role.

Second, we took great care not to denervate the Roux limb by dividing the mesentery. The whole operation is actually done in the area of the duodenum without cutting the mesentery except for 2 cm along the mesenteric border of the jejunum where the anastomoses are done. This may retain normal motility in the Roux limb.

Third, we retained the first portion of the duodenum so that the chyme coming out of the stomach passed over the duodenal mucosa. There may be yet unknown or known hormones that affect the motility when that portion of the gut mucosa is stimulated by chyme. There are a host of possibilities to investigate that may shed some light on the physiology of gastric emptying. The fact that we preserve the duodenal pacemaker has also occurred to us, but this may be of limited value since there is the duodenojejunostomy anastomosis 2–3 cm distal to the pacemaker.

Many of the discussants focused their questions on how we documented the presence of duodenal gastric reflux. First, these 10 patients were selected from 202 patients referred to us specifically with complex foregut symptoms because of our interest in 24-hour pH monitoring. They all complained of nausea, epigastric pain made worse with eating, and bilious vomiting. They all had endoscopic gastritis. All of them had been treated for at least 2 years with a variety of drugs, including H_2 blockers, sucralfate, and/or cholestyramine, and were not adequately relieved of their symptoms in their opinion and ours. It was symptoms that drove the operation.

Because documentation of the disease is such a critical point, I would ask the moderator if I may show two slides. The first slide demonstrates the pH distribution according to time in the stomach (Figure 2 in the manuscript) for normals and one of the patients. Compared with normal subjects, represented by the shaded area, the patient had a shift in the pH of the stomach toward an alkaline side, both during the day and at night. The second slide (Figure 3 in the manuscript) shows the result of a computer-performed discriminant analysis of the pH data to determine the probability that the change in pH was due to duodenal gastric regurgitation and not secondary to a change in gastric motility or acid production. Eight of the 10 patients scored in the pathologic range. It is our belief that this type of technology adds objectivity to the diagnosis of duodenal gastric reflux in patients who have symptoms suggestive of the disease.

Dr. Silen, I appreciate your support by commenting on the long-term follow-up on three patients who had a similar procedure done for treatment of symptomatic duodenal diverticula. The lack of postsurgical ulceration in your patients would support our theory that retention of the proximal duodenum protects against ulcer formation.

Dr. Woodward commented on our measurement of gastric emptying. Our test using oatmeal mixed with a radionucleotide has been standardized against the "gold standard" technique of gastric emptying, that is using livers from chickens injected with the radionucleotide during life. We have found that oatmeal, more than any other substance, correlates closest to the gold standard and is easy to use in the clinic. As you know, it is inconvenient to keep live chickens around to support a routine test.

Lastly, there were a number of comments questioning the existence of duodenal gastric reflux in a primary form. I would like to emphasize that the story of gastric ulcer has never been completed. About two thirds of patients with gastric ulcers have normal or low gastric acidity. The possibility that duodenogastric reflux is a pregastric ulcer condition has been made before. To us it seems that there is a great similarity between this disease and gastroesophageal reflux. Initially, both can have symptoms with little histologic changes; chronically both can cause mucosa changes, ulceration, metaplasia, and neoplasm.

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Use in pregnancy is not recommended except in cases so serious and intractable that, in the physician's judgment, drug intervention is required and potential benefits outweigh possible hazards. There have been instances of prolonged jaundice, extrapyramidal signs, hyperreflexia or hyporeflexia in newborn infants whose mothers received phenothiazines. There is evidence that phenothiazines are excreted in the breast milk of nursing mothers.

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In children with acute illnesses or dehydration, use only under close supervision. Avoid high doses and parenteral administration when cardiovascular system is impaired since hypotension has occurred. Use cautiously in patients with glaucoma. Use with caution in persons who will be exposed to extreme heat since phenothiazines may interfere with thermoregulatory mechanisms. Phenothiazines can diminish the effect of oral anticoagulants. Phenothiazines can produce alpha-adrenergic blockade. Thiazide diuretics may accentuate orthostatic hypotension that may occur with phenothiazines. Antihypertensive effects of guanethidine and related compounds may be counteracted when phenothiazines are used concomitantly. Concomitant administration of phenothiazines with propranolol results in increased plasma levels of both drugs and may also precipitate phenytoin toxicity. Phenothiazines may lower the convulsive threshold; dosage adjustments of anticonvulsants may be necessary. Presence of phenothiazines may produce false positive phenylketonuria (PKU) test results. Patients should not receive 'Compazine' 48 hours before or 24 hours after myelography with the contrast medium metrizamide.

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EKG changes have been reported. Discontinue long-term, high-dose therapy gradually.

Note: Sudden death in patients taking phenothiazines (apparently due to cardiac arrest or asphyxia due to failure of cough reflex) has been reported.

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The Gut Origin Septic States in Blunt Multiple Trauma (ISS = 40) in the ICU

JOHN R. BORDER, M.D., JAMES HASSETT, M.D., JOHN LADUCA, M.D., ROGER SEIBEL, M.D.,
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The association between support elements (ventilator days = Vd, enteral protein = EnP, number of antibiotics per day = AB/d) and the magnitude of the septic state (SSS) and its bacteriologic manifestations (bacti. log) in 66 patients with blunt multiple trauma (mean HTI-ISS = 40) over 1649 days have been studied restrospectively. SSS is measured by summing the standard deviation units of change in the septic direction for the 16 measurements taken every day in the intensive care unit. Increasing Vd is tightly associated with an increasing SSS ($r = +0.52$), after day 10 an increasing bacti. log ($r = +0.21$ to $+0.32$), and an increasing AB/d ($r = +0.26$) (all $p < 0.001$, $N = 1615 - 1626$). The independent variables that best predicted Vd were delayed operations (DORS), day of rising EnP, and total positive blood cultures (TPC) (adj. R sq. = 0.84, F = 104, dF = 3/59). An increasing AB/d was associated with an increasing SSS ($r = +0.38$), increasing Vd ($r = +0.26$), and an increased bacti. log ($r = +0.14$ to $+0.18$) (all $p < 0.001$, $N = 1615$). Only an increased EnP was consistently associated with a reduced SSS ($r = -0.38$) and a reduction in bacti. log ($r = -0.10$ to -0.21) (all $p < 0.001$, $N = 1626$–1636). The independent variables Vd, EnP, AB/d, and TPC best predicted SSS for all surviving patients (adj. R sq. = 0.42, F = 268, dF = 4/1496). The patients who died of sepsis were not different in terms of bacti. log from those with equal Vd but were distinguished by zero EnP, high AB/d, and persistent ventilatory support. In conclusion, DORS is tightly associated with increased Vd, SSS, AB/d, and zero EnP. If Vd exceeds 10, there is an increasing bacti. log and evidence of infection probably from the gut. This responds only to increased EnP and not to AB/d. Death due to sepsis is not associated with increased bacti. log but with zero EnP and high AB/d and their consequences.

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A CRITICALLY INJURED patient after initial treatment seems to become stable or improve for 2–3 days. A severe septic response may then develop with failure of several organs, especially the lung. This is typically treated with broad-spectrum antibiotics on the assumption that hidden infection is present. At about 10 days, bacteriologic evidence of infection develops, which seems to confirm the use of antibiotics earlier. The magnitude of the septic state then largely stabilizes while the bacteriologic evidence of infection gets worse. Repeated changes and additions of antibiotics seem to have little effect on the patient's course. The longer the course, the more likely the patient will die. A large variety of human and animal studies have shown excessive escape of normally confined wound destructive processes in patients and animals with major wounds and sepsis in association with suppression of the normal antibacterial systems (trauma immunology and polymorphonuclear cell literature) and the pulmonary failure (ARDS literature) in a way that suggests cause and effect. These combined observations have tended to confirm the course of the patient with blunt multiple trauma as outlined and to cause almost everyone to accept it as the normal course.

We would suggest that this is not the case and that there are good reasons to believe that the management these patients received in the initial surgical intervention and the subsequent 10 days in the intensive care unit (ICU) causes the pulmonary failure septic state to persist and directly induces the subsequent bacteriologically confirmed infections.[1] We will discuss evidence that bears on this point.

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Methods

This study consists of 66 retrospectively studied patients with blunt multiple trauma (ages 16–60 years) with an injury severity score (ISS) greater than 22 and no documented pre-existing cardiopulmonary hepatic disease who had 2.4 megabytes of data entered for 1649 patient days. This group of patients comprised patients from our study of the effects of fracture fixation on cardiopulmonary metabolic failure in blunt multiple trauma, all blunt multiple trauma patients who stayed in the ICU 14 days or more since 1979, and one patient with detailed metabolic studies who died in 1974. These patients were treated by the physician authors of this paper. All data were entered into the computer for each patient for the entire ICU stay plus data from floor care until the patient was clearly stable. The data consisted of all fluid intake and its contents, all fluid output and its source, all laboratory tests, and all diagnoses and procedures. The day of the hospital stay was used as the key time marker for such entries. All laboratory tests that were repeated within 24 hours were averaged to obtain a single value to characterize the day. At times when a laboratory test was not done, the values of the preceding and following days were averaged and that value was entered for the missing value. All bacteriologic data were entered by source and bacteria cultured for the day the culture was taken. All use and changes of use of antibiotics were recorded by hospital day (AB/d). The conditions of ventilatory support were recorded by hospital day together with the inspired oxygen and positive end expiratory pressure. All delayed operations were recorded by hospital day.

The data were recovered from the chart by three individuals who have had extensive experience recovering data from ICU patient records. These consisted of an experienced ICU head nurse who had worked with these patients (PL), an experienced nurse who has done many such chart reviews and who is also expert in the use of computers (BM), and another person who has 4 years of experience in such chart reviews and the use of the computer (DB). All data were entered into a computer with software specifically designed for the purpose at hand. This data base management system (Datamat®, Transtime Technologies, Tonawanda, NY) allowed conversion of the fluid intake and its components into grams of protein per kilogram per day with a subdivision into route of administration as to intravenous or enteral. The amino acid or protein content entered was based on the label on the substance given and on discussions with the dietitians in charge.

A sepsis severity score (SSS) was then calculated based on the standard deviations of change in the septic direction of the measured variable. The normal range was taken as the mean value plus or minus two standard deviations. The normal range was then divided by four to obtain a standard deviation. The mean normal value was then subtracted from the observed value and the difference divided by a standard deviation to obtain standard deviation units of change. A septic direction of change was defined for each variable. Only the standard deviational units of change in the septic direction were counted in the SSS.

The preceding process was done for each of the 16 observations commonly made every day in the ICU on every patient. The temperature used was the maximum temperature of the day. The other observations were electrolytes, blood gases, creatinine, glucose, bilirubin, WBC, platelets, and positive end expiratory pressure (PEEP). PEEP was entered directly as centimeters of water. The alveolar arterial oxygen tension difference ($A\text{-}aD_{O2}$) was calculated from the inspired oxygen and the arterial oxygen tension and then corrected for standard deviational units by the increase in $A\text{-}aD_{O2}$ that occurs in the normal lung with an increase in the inspired oxygen. Since the lung was characterized in terms of the septic response by three characteristics (PO_2, $A\text{-}aD_{O2}$, and PEEP), the contribution of the lung to the septic response was triple weighted.

The standard deviations in the septic direction for each of the 16 observations considered were then summed to give the SSS. No weight was given to changes in an observation from the mean in the direction opposite to the septic direction. Thus, leukopenia, for instance, was not considered.

Some observations have narrow normal ranges and some have wide normal ranges. This characteristic resulted in some observations giving a far smaller contribution in standard deviations (*e.g.,* temperature) than the weight the clinician would give such an observation and other observations giving far more standard deviations than the weight the clinician would give such an observation (*e.g.,* creatinine and bilirubin). Constant multipliers and dividers were then introduced until each observation for a patient with maximal sepsis had approximately the same weight in standard deviations.

The normal range of SSS is from 0 (all 16 variables at the proper mean value) to 32 (all 16 variables at the outer limit of normal).

The patients were divided into groups based on their duration of stay in the ICU. Group 1 stayed 3–7 days, Group 2 stayed 8–14 days, Group 3 stayed 15–21 days, Group 4 stayed 22–28 days, Group 5 stayed 29–135 days, and all patients in Group 6 died of sepsis at 22–43 days in the ICU. This division produced roughly equal numbers for the various groups (Group 1, N = 11; Group 2, N = 14; Group 3, N = 12; Group 4, N = 13; Group 5, N = 12; and Group 6, N = 4). To maintain a

TABLE 1. *Demographic Data (Mean ± SD)*

Group	N	Age (Years)	ISS	No. of Diagnoses	No. of Procedures	No. of + Cultures	No. of Blood Cultures Taken	No. of + Blood Cultures	Ventilator Days	Total Days ICU	Total Hospital Days
All	66	29 ± 12	40 ± 11	14 ± 6	12 ± 8	16 ± 20	10 ± 12	2.3 ± 6	17 ± 21	25 ± 24	67 ± 62
1	11	24 ± 9	38 ± 6	11 ± 5	8 ± 3	1.4 ± 1.5*	1.3 ± 2.1*	0 ± 0*	2 ± 2*	5 ± 1*	41 ± 13*
2	13	28 ± 11	40 ± 7	14 ± 6	10 ± 3	2.8 ± 2.8*	2.4 ± 3.8*	0.1 ± 0.3*	6 ± 3*	11 ± 2*	43 ± 25*
3	12	31 ± 14	41 ± 12	15 ± 7	12 ± 6	5.7 ± 5*	6.6 ± 6.3*	0.5 ± 0.7*	8 ± 6*	18 ± 3*	46 ± 15*
4	13	31 ± 13	38 ± 12	13 ± 5	12 ± 7	16 ± 11.2*	8.1 ± 5.9*	1.0 ± 1.4*	16 ± 7*	28 ± 4*	96 ± 110*
5	13	29 ± 13	42 ± 11	17 ± 6	16 ± 12	46 ± 22.1*	27.6 ± 14.3*	9.5 ± 11*	45 ± 31*	63 ± 29*	113 ± 48*
6	4	36 ± 10	54 ± 13	16 ± 2	13 ± 9	26 ± 16.2*	16 ± 9*	2.2 ± 1.5*	28 ± 11*	29 ± 11*	32 ± 10*

*Statistically significant difference among Groups 1–6, F range 4.1–29.4, $p < 0.001$.

constant N for statistical comparison of the groups, the study period was ended when half of the patients had been discharged from the ICU. Mean values were then used to fill the data base from the time of earliest discharge to the time when one half of the patients had been discharged. Data without this mean value fill are shown in many places subsequently (see especially Tables 10–16 and Figures 1–3, 6, 12, and 14). This procedure was followed only for those patients who continued to do well and did not return to the ICU for further care. In those patients who were discharged from the ICU and returned for further critical care, the patient was entered into the group that corresponded to his final discharge from the ICU, and no attempt was made to fill missing data.

Results

Table 1 shows the characteristics of the patients in means and standard deviations for all 66 patients as a single group and for each of the subgroups. The mean age is 29 years mean ISS is 40, mean number of diagnoses is 14, mean number of procedures is 12, mean days on the ventilator is 17, and mean days in the ICU is 25. At the bottom of the table is the analysis of variance between the groups. By this statistic, the groups are identical in age, ISS, sex, and the number of diagnoses and procedures, and differ at a statistically significant level in ventilator days (Vd), ICU days (TICUd), hospital days (THd), total cultures taken (TCT), total positive cultures (TPC), total blood cultures taken (TBCT), and total positive blood cultures (TPBC). The primary determinants of increased TICUd are the number of delayed operations, the day of rising enteral protein intake (REI), and the TPC (see Fig. 15). The correlation between ICU days and ventilator days is +0.92 ($p < 0.001$).

Table 2 shows the Pearson cross-correlations for the SSS to its components arranged by the magnitude of r for all observations on all 66 patients. It is to be noted that platelets have a nonsignificant correlation.

Table 3 shows the changing relationships with time of SSS to its components as judged by Pearson correlations. The time scale is 0–3 days, 3–10 days, and the period of REI for Groups 1–5. It is to be noted that the SSS components A-aD_{O2}, plate., CO_2v, glucose, creatinine, Vd, do not have a changing relationship with time to SSS. The SSS components and support variables that do not have a significant correlation on days 0–3 that later have significant correlations are PO_2, Na+, Cl−, bilirubin, albumin, EnP, IVP, TBCT, TPC, and TPBC. These abbreviations are as follows: (1) EnP = enteral protein in grams per kilogram per day and (2) IVP = intravenous protein or amino acids for the same dimension as EnP. The variables that develop an increasingly significant correlation and magnitude of correlation with the passage of time are EnP, PEEP, albumin, Cl−, Na+, WBC, pH, PO_2, TCT, TBCT, TPC, and TPBC. PCO_2 and K+ have a progressive negative relationship with the passage of time, whereas bilirubin has a biphasic relationship to time.

Table 4 shows the results of a stepwise linear regression of SSS to its components. Only 10 of 16 variables

TABLE 2. *Pearson Correlation Coefficients, Relationship between SSS and its Components**

Variable	r
PEEP	+0.58
Creatinine	+0.58
A-aD_{O_2}	+0.54
Glucose	+0.51
Chloride	+0.51
Temperature	+0.50
Bilirubin	+0.49
WBC	+0.46
Venous CO_2	+0.43
pH	+0.41
Albumin	+0.31
PCO_2	+0.25
Potassium	+0.20
Sodium	+0.14
PO_2	+0.12

* $N = 1480$, $p < 0.001$. Platelets: not significant.

TABLE 3. *Pearson Correlation Coefficients, SSS with its Components, Protein Intake, Ventilator Days, and Bacteriology Data and their Changing Relationship with Time*

	Protein		SSS Components										Bacteriology: No. per Patient			
Time	Enteral	IV	PEEP	pH	PO_2	PCO_2	Albumin	WBC	Chloride	Sodium	Potassium	Bilirubin†	Cultures Taken	+ Cultures	Blood Cultures Taken	+ Blood Cultures
0-3 (N = 195)	−0.01	−0.02	+0.37*	+0.20*	+0.02	+0.29*	+0.11	+0.31*	+0.16	−0.04	+0.30*	+0.07	+0.20*	+0.14	+0.17	+0.07
3-10 (N = 490)	−0.26*	+0.18	+0.53*	+0.18*	+0.12	+0.17*	+0.30*	+0.44*	+0.27*	+0.13*	+0.28*	+0.43*	+0.39*	+0.33*	+0.31*	+0.23*
REI† (N = 1043)	−0.29*	+0.24*	+0.63*	+0.32*	+0.12*	+0.21*	+0.39*	+0.51*	+0.33*	+0.20*	+0.06	+0.21*	+0.33*	+0.33*	+0.33*	+0.26*

* $p < 0.01$.
† Bilirubin has a biphasic relationship to SSS.
REI Group 1 Days 3–7, Group 2 Days 5–14, Group 3 Days 6–21, Group 4 Days 5–28, Group 5 Days 11–50.

Variables whose coefficients remained significantly high ($p < 0.001$), throughout all time periods: A-aD_{O2}, venous CO_2, glucose, creatinine, temperature, and ventilator days.
Platelets remained insignificant throughout.

are required to reach an adjusted R2 of 0.986 and an F of 10,604. The variables not in the equation at step 10 are CO_2v, K+, Plate., pH, pCO_2, and PO_2. This analysis states that we could have adequately measured SSS by the use of the 10 remaining variables and that in this group of variables the leading role is played by PEEP, creatinine, glucose, bilirubin, A-aD_{O2} and WBC. It also shows that statistically we were able to maintain oxygen transport.

Table 5 shows the Pearson cross-correlations between the SSS for all days on all patients for EnP, Vd, IVP, TBCT, TPBC, TCT, and total nasogastric suction volume (TNG). SSS is tightly and positively correlated with all measures except EnP, which is negatively correlated. Finally, nasogastric suction volume increases with an increasing SSS as most clinicians would have suspected.

Table 6 compares the Pearson cross-correlations for EnP and Vd with the bacteriology log, Vd, FFP, and TRBC. All EnP correlations are highly significant and negative, whereas all Vd correlations are highly significant and positive. Increasing EnP is associated with decreasing use of red cells (TRBC) and fresh frozen plasma (FFP), whereas increasing Vd is associated with increasing use of these support elements. EnP has a negative correlation with Vd. Table 7 compares the Pearson cross-correlations of EnP and Vd for all patients with SSS and the seven major components of SSS. Again, all EnP correlations are highly significant and negative, whereas all Vd correlations are equally significant and positive.

Table 8 shows the Pearson correlations of the number of antibiotics per day (AB/d). There are positive highly significant correlations with SSS, Vd, IVP, and the components of the bacteriology log, and only EnP has a highly significant negative correlation. The bacteriology correlations are of smaller magnitude than the other correlations. If antibiotics were effective in the presumed way, the bacteriology log correlations should be negative. Table 9 shows the Pearson correlations to TPC of SSS, the bacteriology log, and AB/d. These are all highly significant and positive, with the smallest numerical value for AB/d. Again, the AB/d correlations should be negative if they had the effect desired.

Table 10 shows the initial characteristics for a patient grouping based on the first 20 days with no enteral protein (N = 10), minimal enteral protein (N = 9), and the rest of the patients in the ICU the same length of time (N = 8). The initial characteristics of those patients are not statistically different by ANOVA, but they differ significantly for Vd per group with the greatest number for the group with no enteral protein.

Table 11 shows the associations between no enteral protein, minimal enteral protein, and normal enteral protein for the first 20 days of the hospital course expressed for the table as the mean per patient day. These comparisons exclude the patients in the ICU less than 20 days. The reference group (A) has 0.61 g protein/kg/day plus 0.48 g intravenous protein/kg/day (total 1.09), whereas the minimal enteral protein group (B) has 0.110 + 1.40 (total 1.51) and the no enteral protein group (C) has 0.01 + 1.820 (total 1.82). Thus, total protein intake per kilogram per day increases as enteral protein intake decreases. In association with these changes, SSS increases from group A (48) to group B (55.5) to group C (73.6) at a highly significant level statistically ($p < 0.0001$). In addition, all bacteriology log measurements increase at a highly significant level statistically from group A to C and total positive blood cultures from group A to B or C. Figure 1 shows SSS by day as the mean per group for the reference group (A) and the no enteral protein group (C) plus mean daily EnP and total protein (TP) for a 6–21-day period. The two groups begin at the same SSS and the difference in SSS continually evolves over the 20 days of observation. Thus, the absence of enteral protein intake is associated with progressively more septic behavior by all criteria, and this is not compensated for by increased intravenous protein support, which provides almost twice as much protein.

Table 12 shows the characteristics of a group of patients left in femoral traction for 21 days relative to a control group of patients who had open reduction and internal fixation of their fractures initially or after femur traction up to 9 days. There is no statistically significant

TABLE 4. *Stepwise Multiple Linear Regression, The Components of SSS that are its Best Predictors**

Step	Variable	Adj R^2	F
1	PEEP	0.34	769
2	Creatinine	0.53	820
3	Glucose	0.70	1148
4	WBC	0.79	1366
5	Bilirubin	0.87	1898
6	A-aD_{O_2}	0.91	2566
7	Albumin	0.94	3455
8	Chloride	0.96	4910
9	Temperature	0.98	9186
10	Sodium	0.99	10604

* df = 1468, Standard error = 2.4, $p < 0.001$.
Variables not in the regression: venous CO_2, potassium, platelets, pH, PCO_2, PO_2.

TABLE 5. *Pearson Correlation Coefficients between SSS and the Following**

		r
Enteral protein g/kg	(EnP)	−0.38
Ventilator days	(Vd)	+0.52
IV protein (g/kg)	(IVP)	+0.32
Blood cultures taken	(TBCT)	+0.30
+ Blood cultures	(TPBC)	+0.21
Cultures Taken	(TCT)	+0.33
+ Cultures	(TPC)	+0.32
Nasogastric output	(TNG)	+0.41

* N = 1626, $p < 0.001$.

TABLE 6. *Pearson Correlation Coefficients, Enteral Support and Ventilator Days**

	Enteral Protein (g/kg)	Ventilator Days
Cultures taken	−0.21	+0.30
+ Cultures	−0.18	+0.26
Blood cultures taken	−0.16	+0.25
+ Blood cultures	−0.10	+0.12
Ventilator days	−0.48	1.00
Fresh frozen plasma	−0.24	+0.21
Packed red cells	−0.23	+0.19

* N = 1636, $p < 0.001$.

TABLE 7. *Pearson Correlation Coefficients, SSS Components to Enteral Protein and Ventilator Days**

	Enteral Protein (g/kg)	Ventilator Days
PEEP	−0.38	+0.70
Temperature	−0.17	+0.31
A-aD_{O_2}	−0.26	+0.28
Glucose	−0.23	+0.23
Bilirubin	−0.24	+0.19
Creatinine	−0.10	+0.18

* N = 1475, $p < 0.001$.

TABLE 8. *Pearson Correlation Coefficients between Antibiotics/Day and the Following**

	r
SSS	+0.38
Ventilator days	+0.26
Enteral protein	−0.25
IV protein	+0.28
Cultures taken	+0.18
Blood cultures taken	+0.16
+ Cultures	+0.15
+ Blood cultures	+0.14

* N = 1615, $p < 0.001$.

TABLE 9. *Pearson Correlation Coefficients, Relationship between Number Positive Cultures per Day and the Following**

	r
SSS	+0.32
Cultures taken	+0.84
Blood cultures taken	+0.52
+ Blood cultures	+0.56
Antibiotics/Day	+0.15

* N = 1620, $p < 0.001$.

TABLE 10. *The Effects of No Enteral Protein for 20 Days: A Comparison of the Initial Characteristics of Each Group (Mean ± SD)**

Group	N	ISS	Age (Years)	No. of Diagnoses	No. of Procedures	Ventilator Days (TVd)
Control group	8	38.0 ± 12.5	27.0 ± 8.9	14.0 ± 5.0	12.6 ± 8.1	13.0 ± 4.6†
Minimal enteral protein	9	45.5 ± 13.6	32.7 ± 14.0	16.4 ± 5.3	16.4 ± 12.5	26.0 ± 23.0†
No enteral protein	10	44.7 ± 12.6	29.6 ± 13.4	16.8 ± 4.8	11.8 ± 5.6	43.0 ± 32.0†

* ANOVA = no statistically significant differences for ISS, age, number of diagnoses and procedures.

† Significantly different, p < 0.04.

TABLE 11. *The Effects of No Enteral Protein during the First 20 days (Mean ± SD)**

					Mean per Patient Day			
Group	N	Enteral Protein (g/kg)	SSS	IV Protein (g/kg)	Cultures Taken	Blood Cultures Taken	Positive Cultures	+ Blood Cultures
Control group	8	0.61 ± 0.55	48.0 ± 11.5	0.47 ± 0.64	1.04 ± 1.64	0.28 ± 0.68	0.51 ± 0.93	0.03 ± 0.23
Minimal enteral protein	9	0.11 ± 0.21	55.5 ± 12.9	1.40 ± 1.10	1.40 ± 2.19	0.51 ± 0.97	0.71 ± 1.32	0.15 ± 0.52
No enteral protein	10	0.01 ± 0.03	73.6 ± 26.1	1.82 ± 1.13	2.46 ± 2.54	0.88 ± 1.17	1.29 ± 1.73	0.27 ± 0.76

* ANOVA reveals statistically significant differences between groups for all comparisons at p < 0.000.

difference in the groups for age, ISS, or the number of diagnoses or procedures.

Table 13 shows the effect of 21 days of traction on these patients in terms of mean values per patient day for 21 days. SSS is statistically significantly higher (72 *vs.* 47, p < 0.000), whereas EnP is lower (0.14 *vs.* 0.39, p < 0.000) and IVP (0.87 *vs.* 1.11) and TP (1.00 *vs.* 1.49) are also significantly lower (p < 0.04 and 0.000). The components of the bacteriology log and SSS are all increased with traction at a significant level (p < 0.006). Figure 2 shows SSS by day per group for these two groups and the mean EnP and TP for days 6–21. It is apparent that SSS for the group in traction progressively rises, whereas SSS is stable for the group with ORIF and no traction.

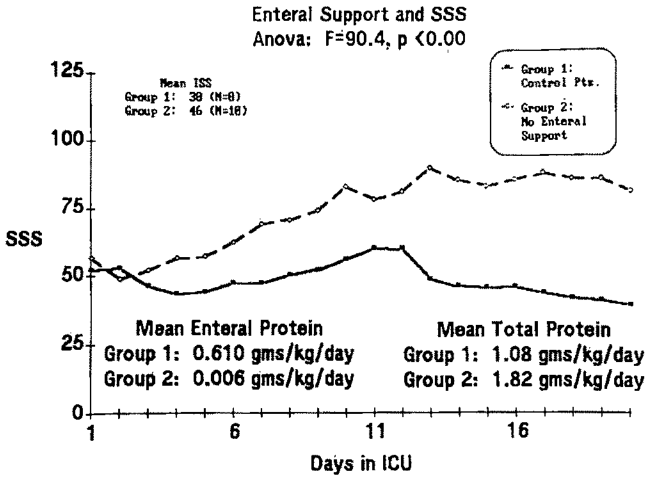

FIG. 1. A comparison of the associations of zero EnP or 0.61 g of EnP with SSS on a group daily mean basis. See Tables 10 and 11 for further details. The group with zero EnP has a progressively rising SSS, whereas the group with 0.61 g of EnP has a stable to falling SSS over the 21 days of observations. The group with zero EnP receives much more total protein (1.82 *vs.* 1.08 g). There is no mean data fill in this comparison.

Table 14 shows the characteristics of groups of patients who have 0–2 delayed operations *versus* those who had 3 or more delayed operations. Age, ISS, and the number of diagnoses are statistically identical, whereas the number of procedures, ICU days, and Vd are increased at statistically significant levels (p < 0.02).

Table 15 shows the effect of delayed operations on these patients by mean values per patient day for SSS, EnP, IVP, and the components of the bacteriology log. Three or more delayed operations are associated with a higher SSS score (60.3 *vs.* 46.54), a lower EnP (0.24 *vs.* 0.41), a higher IVP (1.27 *vs.* 1.06), and an increase in all components of the bacteriology log (p < 0.001). Figure 3 shows SSS by day per group and mean EnP and TP for days 6–21. It is apparent that SSS for those with three or more delayed operations rises from days 1–10 relative to the other group and is then consistently greater.

SSS when analyzed for days 0–3 for all six groups is not statistically different among the groups by ANOVA (Fig. 4). The primary difference in SSS among groups arises in days 3–10. This changing relationship is further discussed in the section dealing with stepwise linear regression.

The relationships of IVP and SSS for the five surviving groups (constant N, mean data fill) are shown in Figure 4. The positive correlation between the magnitude of the septic state as judged by SSS and IVP per kilogram is in major part our therapeutic response to the septic state. Figure 5 shows the relationship of EnP to

TABLE 12. *Open Reduction and Internal Fixation of Femur Fractures (ORIF)* Versus *Traction for Femur Fractures: A Comparison of the Initial Characteristics of Each Group (Mean ± SD)**

Group	N	ISS	Age	No. of Diagnoses	No. of Procedures
ORIF femur fractures	47	40.0 ± 10.0	29.0 ± 12.2	13.8 ± 5.4	11.2 ± 16.8
Traction for femur fractures	4	42.5 ± 18.9	32.0 ± 18.0	17.0 ± 4.7	16.8 ± 10.8

* No statistically significant differences between the groups.

TABLE 13. *Effects of Traction* Versus *Open Reduction and Internal Fixation (ORIF) of Femur Fractures on the Following (Mean ± SD)**

					Mean per Patient Day			
Group	N	Enteral Protein (g/kg)	SSS	IV Protein (g/kg)	Cultures Taken	Blood Cultures Taken	Positive Cultures	+ Blood Cultures
ORIF femur fractures	47	0.39 ± 0.54	47.0 ± 14.4	1.11 ± 1.08	1.04 ± 1.88	0.30 ± 0.74	0.53 ± 1.19	0.08 ± 0.44
Traction femur fractures	4	0.14 ± 0.29	72.0 ± 26.0	0.87 ± 0.65	2.40 ± 2.40	0.86 ± 1.05	1.40 ± 1.76	0.28 ± 0.62

* Significant differences, all comparisons p < 0.006.

SSS for all five surviving groups (constant N, mean data fill). The tight association between falling SSS and REI is immediately obvious. Group 5 patients, who were the most septic for the longest time, received about 2.5 g total protein/kg/day in association with their survival. This intake was achieved with orders for 3.5–4 g of protein.

Figure 6 shows SSS as a function of days on the ventilator for each surviving group with variable N (no mean data fill) as they came off. It shows the values obtained only when the patient was on the ventilator and excludes all other values. The high SSS values, achieved in Groups 1–4 by day 10, remain stable and decline rather preciptiously near the end of the ICU stay. This does not occur in Group 5. In the lower panel, the declines in SSS are tightly associated with REI in Groups 2–4, even for those patients remaining on the ventilator. Even in Group 5 the expected relationship between EnP and SSS exists but there is no abrupt rise in EnP as there is in the other groups.

Figure 7 shows the effect of severe but survivable head injury in patients with multiple trauma on SSS, EnP, and IVP. It is apparent that in the first 4 days SSS is much higher than that shown in Figures 4 or 5, but that there is little effect after the first 4 days and that the relationship to enteral protein exists here as elsewhere.

Figure 8 shows the fluid volumes associated with this sort of exogenous protein support for all surviving patients by day with variable N. It is apparent that the typical patient receives about 4500 mL/day on all days, which is composed of an increasing enteral intake and decreasing intravenous intake. The same figure shows a urine output of about 3000 mL/day. Oliguric renal failure occurred in one surviving patient.

Tables 16 and 17 show the effect of a change in antibiotic on SSS and blood bacteria. The effect of a change in antibiotics was tested by excluding the first 10 days of the courses (rising SSS period and the period of REI [falling SSS period]). Twenty-seven comparisons of the 3 days of SSS before and after a change in antibiotics were conducted using a paired t-test on mean values. There was no significant change in SSS associated with the change in antibiotic, and at the same time there was no significant change in EnP, IVP, or temperature. Table 17 explores the effect of a change in antibiotic on the blood bacteria using a forward 3-day window to observe

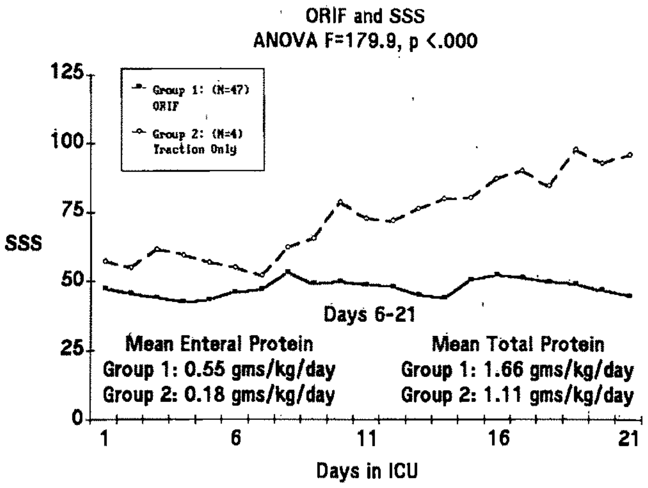

FIG 2. A comparison of the associations of femoral fracture internal fixation or femur traction over 21 days with the group daily mean SSS. See Tables 12 and 13 or more details. The group with femur traction has a progressively increasing SSS over the 21-day period relative to the stable or falling SSS of those with internal fixation. See also our previous report.[1] There is no mean data fill in this comparison.

TABLE 14. *Delayed Surgery: A Comparison of the Initial Characteristics of Each Group (Mean ± SD)*

Group	N	ISS	Age	No. of Diagnoses	No. of Procedures	ICU Days	Ventilator Days
0–2 delayed operations	39	39.5 ± 10.1	28.9 ± 12.4	14.1 ± 5.7	10.1 ± 5.6*	15.8 ± 9.5*	9.4 ± 8.5*
>3 delayed operations	27	42.6 ± 11.3	29.1 ± 11.7	14.9 ± 5.7	15.0 ± 9.2*	40.6 ± 29.9*	27.7 ± 28.2*

* Significantly different, $p < 0.02$.

TABLE 15. *The Effects of Delayed Operations (Mean ± SD)**

					Mean per Patient Day			
Group	N	Enteral Protein (g/kg)	SSS	IV Protein (g/kg)	Cultures Taken	Blood Cultures Taken	Positive Cultures	+ Blood Cultures
0–2 delayed operations	39	0.41 ± 0.54	46.5 ± 14.6	1.06 ± 1.17	0.98 ± 1.74	0.29 ± 0.75	0.42 ± 0.89	0.03 ± 0.19
>3 delayed operations	27	0.24 ± 0.43	60.3 ± 23.0	1.27 ± 0.95	1.55 ± 2.24	0.51 ± 0.94	0.82 ± 1.44	0.16 ± 0.57

* All comparisons significantly different at $p < 0.001$.

for change in the blood bacteria in the 30 patients who had positive blood cultures. A positive change was defined as the disappearance of bacteria within 3 days of an added antibiotic or the appearance of new bacteria within 3 days of stopping an antibiotic. A negative change was defined as the appearance of new bacteria in the presence of an added antibiotic within 3 days. This provides for twice as many positive as negative correlations. The data show that these patients have many changes of both antibiotics and bacteria, but that there is an equal association of positive and negative blood bacteria changes in a forward 3-day window with an antibiotic change. There is no evidence to support a beneficial effect of antibiotics on the septic state in terms of changes in blood bacteria in this particular cohort of patients.

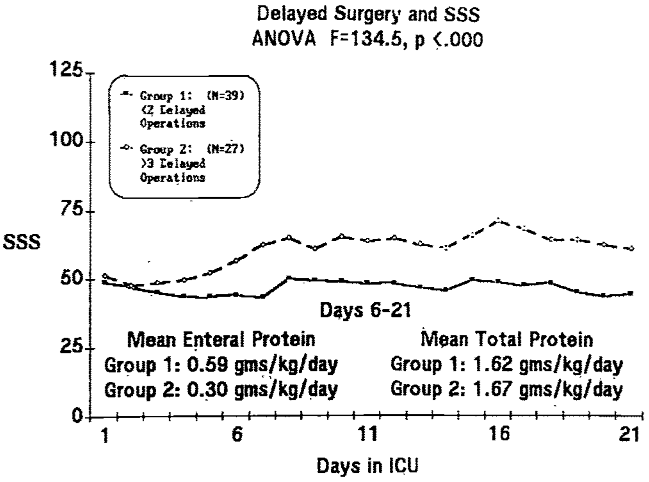

FIG. 3. A comparison of the association of various numbers of operations (0–2 *vs.* 3 or more) with SSS. See Tables 14 and 15 for more details. It is to be observed that 3 or more delayed operations are associated with a persistently higher SSS than 0–2 delayed operations. See Figure 14 for the effects of delayed operations on ICU days. ICU days correlates tightly ($r = 0.92$, $N = 62$, $p < 0.001$) with ventilator days. See Tables 5, 6, and 7 for the association of Vd with SSS, bacti. log, and components of SSS. There is no mean data fill in the comparison.

The patients who died of sepsis (Group 6) had a rise in SSS of 110 to 130 in association with an average of two positive blood cultures of 16 taken. The rise in SSS that led to death is shown for three of four patients in Figure 9 as a function of time. Two of these patients received large amounts of intravenous protein, and two received totally inadequate total protein by the standards of Group 5. Three of the four patients received no enteral protein support (shown in Fig. 9) and the fourth patient received little total protein support for a prolonged pe-

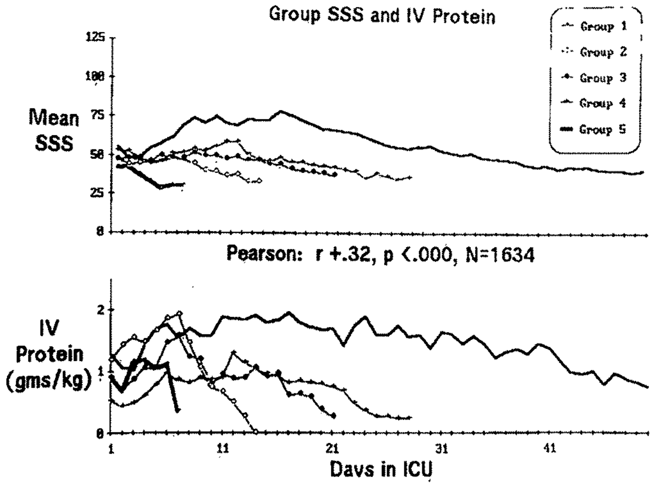

FIG. 4. A comparison of SSS by group to IVP by group daily mean. It is obvious that the two curves are parallel as shown by the Pearson correlation data. This is a result of our therapeutic response to the septic state.

riod and then increasing enteral protein in the premortem phase when her lungs were in severe failure. This patient was in traction at all times and was discharged from the ICU and then returned to the ICU. The results for this patient are shown in Figure 10. This patient had an ISS of 36 with an acetabular fracture that was treated in traction, operated on inadequately 7 days later, and as a result received continued traction until death. She received little protein *via* any route until she was close to death. She died of multiple systems organ failure due to severe protein malnutrition with failure of the lungs as an oxygen transport organ as a major component. She had four positive blood cultures for *Staphylococcus epidermidis* in her terminal phase. Figure 11 shows values for a patient who died in 1974.[16,17] The values for this patient are shown because we have reported on the patient's death metabolically in great detail. At day 10 his splanchnic extraction of glutamine went to zero and concurrently the SSS rapidly rose. At day 17, the splanchnic extraction of isoleucine and methionine also went to zero. From day 10 to day 17, the SSS continued to rise rapidly. This patient also received no enteral protein and grossly inadequate total protein. Death occurred from multiple systems organ failure.

The patients who died of sepsis had an average of two positive blood cultures, whereas the patients of Group 5, all of whom lived, had an average of eleven positive blood cultures. We have shown that increasing Vd is tightly associated with an increasing number of positive blood cultures. Figure 12 plots group mean positive blood cultures per patient ventilator day by group mean ventilator days to compensate for the different numbers

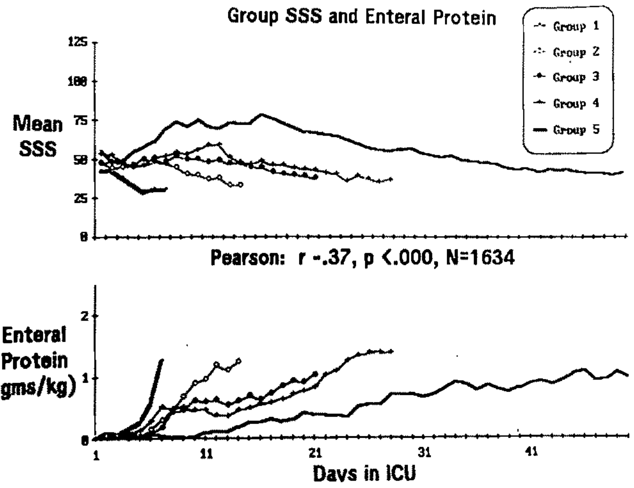

FIG. 5. A comparison of SSS by group daily mean to EnP by group daily mean. This data base has a constant N per group achieved with a mean data fill between the time of earliest ventilator weaning in a given group to the time when one half the patients had been discharged from the ICU. The relationship of a rising EnP to a falling SSS for each group is obvious and confirms the Pearson correlations.

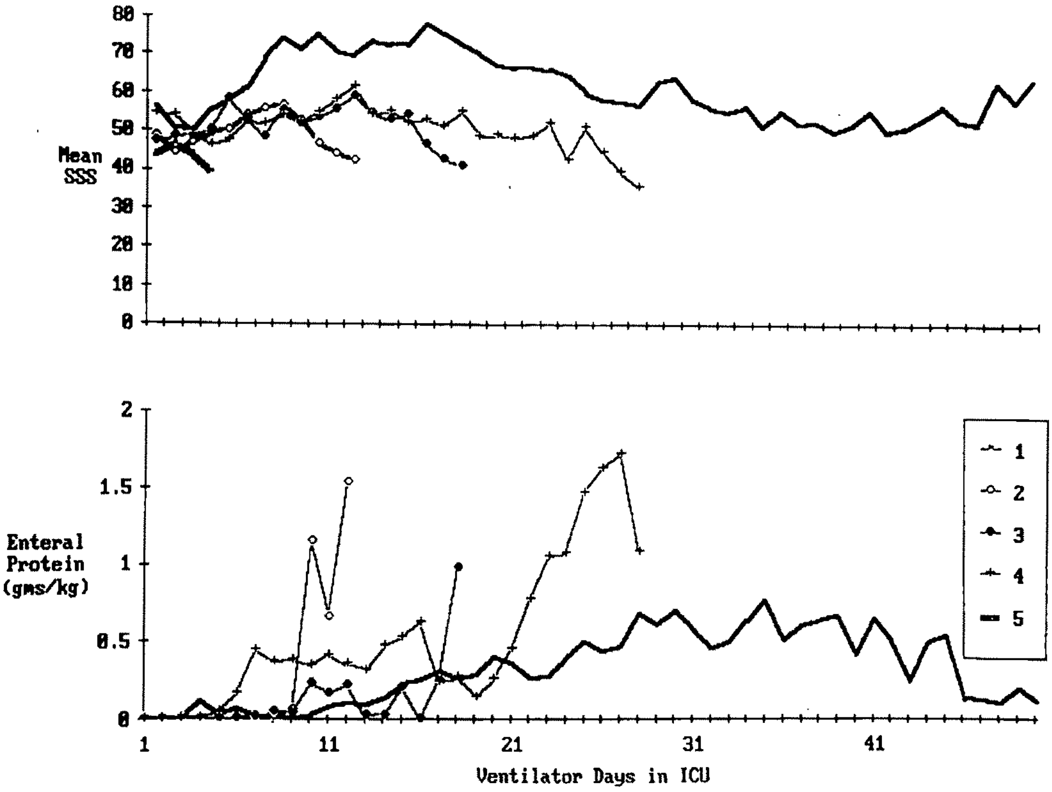

FIG. 6. A comparison by group of SSS and EnP daily mean values for those patients still on the ventilator. This produces a variable N as the patients are weaned but has no mean data fill. SSS in each group after the initial 10 days is stable and falls abruptly in Groups 2–4 as EnP rises rapidly. This occurs when they are gotten out of bed and sitting up while on the ventilator. Group 1 is sitting up out of bed at 2–3 days and the patients eat after coming off the ventilator. Group 5 has the expected reciprocal relationship between SSS and EnP but does not have the rapid rise in EnP that Groups 2–4 have.

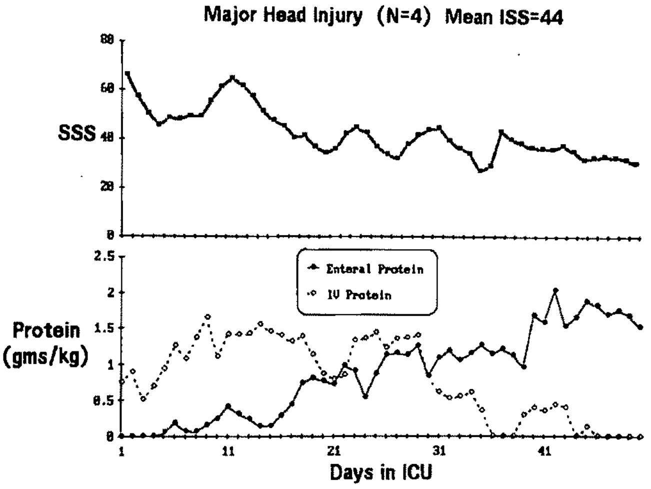

FIG. 7. Major but survivable head injury and its effects on SSS, IVP, and EnP. It is apparent that SSS is very high but declining in the first 4–5 days. After that time, the behavior of SSS and ENP is the same as the other groups.

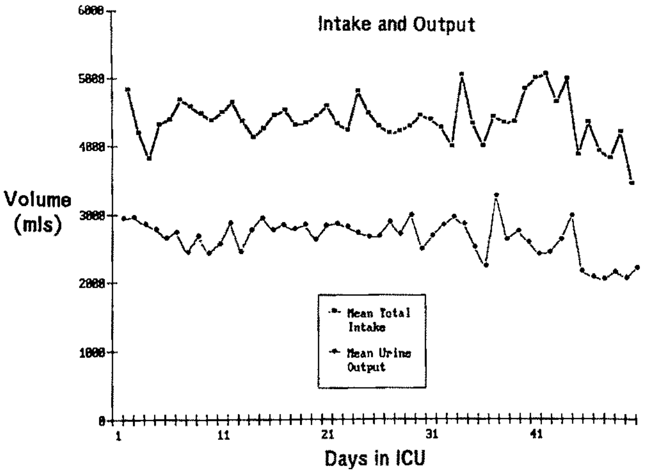

FIG. 8. Intake and output with variable N. These patients received 4500–5000 mL of fluid intake per day and had 2500–3000 mL of urine output per day. On this regimen, oxygen transport was well maintained statistically (see Table 4) and oliguric renal failure did not occur. This regimen results from the fluid volumes necessary to deliver 2–2.5 g protein/kg/day.

of ventilator days among groups. It is immediately apparent that an increasing number of ventilator days is tightly associated with an increasing number of positive blood cultures per patient ventilator day beginning at day 9 (Group 3) and that the group of patients that died of sepsis (Group 6) had the appropriate number of positive blood cultures for the number of days they spent on the ventilator as extrapolated from the surviving patients. Group 6 is not different from the surviving groups by this bacteriologic measure.

Table 18 shows SSS for a day of a positive blood culture, a day of a negative blood culture, and all days without a positive blood culture. SSS is statistically significantly greater on a day of a positive blood culture compared with a day of a negative blood culture or a day without a positive culture. The increase in SSS from a day of a negative blood culture to a positive blood culture is not a clinically significant increase, but the increase in SSS from no positive blood culture to a positive blood culture is both statistically and clinically significant.

One must deduce that blood cultures are taken in the septic patient, and that they are positive makes only a slight additional contribution to the septic state.

Table 19 lists the number of patients per group, the

TABLE 16. *A Comparison of 3 days before and 3 days after a Change in Antibiotic Therapy is Noted: Effects on Septic Severity Score, Temperature, Enteral and IV Protein Intake (Mean ± SD)**

	N	Septic Severity Score (SSS)	Enteral Protein (g/kg)	IV Protein (g/kg)	Temperature
3 days before change	27	74.5 ± 25.0	0.15 ± 0.28	1.79 ± 1.08	38.9 ± 0.8
3 days after change	27	71.5 ± 24.0	0.20 ± 0.34	1.89 ± 1.31	38.9 ± 0.8

* Days excluded: first 10 days and days of rising enteral intake. No significant differences observed.

TABLE 17. *The Effects of Changes in Antibiotic Therapy on Blood Bacteria in 30 Patients in a Forward 3-day Window (Mean ± SD)**

Mean antibiotic changes per patient		5.33 ± 3.38
Mean blood bacteria changes per patient		5.67 ± 6.29
Positive correlations	Number of times blood bacteria disappeared (as expected) when a new antibiotic was added *or* number of times blood bacteria appeared after an antibiotic was discontinued.	0.93 ± 1.26
Negative correlations	Number of times new bacteria appeared with the addition of a new antibiotic.	0.80 ± 1.00

* By definition, positive correlations have a probability of *2 times* negative correlations. No significant change observed.

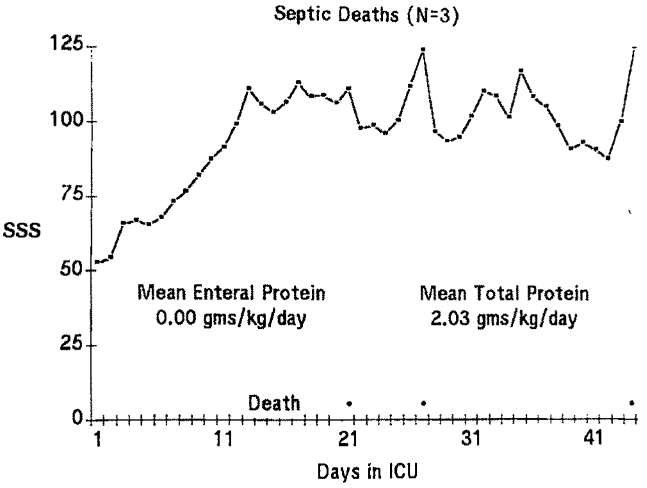

FIG. 9. This shows the behavior of SSS in the three patients who died with zero EnP. The hospital days of their deaths are noted at the bottom. Death is associated with an SSS between 100 and 125 and occurs earliest in the patient who received the least exogenous protein.

number of patients with positive blood cultures per group, the total blood cultures taken per patient in each group, the total positive blood cultures per patient per group, and the total match of blood bacteria to any other culture report from any other site per patient with a positive blood culture. We have excluded from the table those organisms most commonly believed to come from the gut, which are Candida, *S. epidermidis*, and Pseudomonas. The fraction of patients per group with a positive blood culture increases with increasing time in the ICU on the ventilator. In the 21–28-day period, this reaches 50% (Groups 3 and 4). In the period greater than 28 days, it reaches 100% (Group 5). Total blood cultures taken per patient also increase in direct proportion to the number of days in the ICU. The percentage of blood cultures taken that are positive remains consistently less than 35% but rises rapidly from Group 2 (4%) to Group 3 (12%) to group 4 (17%) to group 5 (35%). The match of the blood bacteria to other sites reported in a plus or minus 3-day window also rises rapidly from 0.2 in Group 3, (days 14–21), to 2.4 in Group 4, (days 21–28), to 4.1 in Group 5 (days 28–135). Thus, with increasing time on the ventilator, there is increasing bacteriologic evidence of infection in sites other than the blood as well as in the blood.

Group 6 comprised the patients who died of sepsis. These patients all had one to four positive blood cultures (mean: 2.2 of 16 taken) that were primarily obtained just before death. The number of positive blood cultures obtained per patient in this group was the number to be expected for the days these patients spent on the ventilator as extrapolated from the surviving patients (cf. Group 4 here and Figure 12). The match of the blood bacteria to any other site report in a plus or minus 3-day window is also that expected from Group 4 (1.5 *vs.* 2.4). In fact, compared with Group 4, the percentage of positive blood cultures of those taken is also approximately the same for Group 6 (13.7%; Group 4, 17.3%).

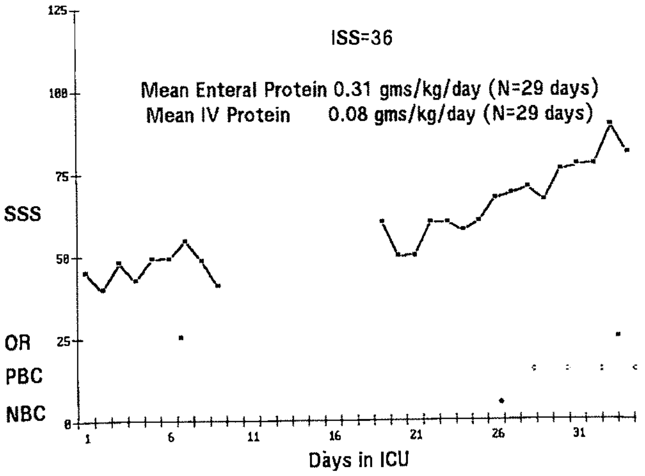

FIG. 10. This shows the SSS of the patient who died in association with continued femoral traction for an acetabular fracture. It represents a typical late septic death from conservative fracture management. The patient seems to get better and is discharged from the ICU. The doctors assumed that the patient is doing well, whereas the nurses' notes are filled with reports of the patient not eating. She receives no nutritional support for almost 26 days after injury and several days after she re-enters the ICU in crisis. As she is dying of failure of her lungs as an oxygen transport organ and multiple systems organ failure, she is given enteral protein when it is too late. OR = operation, NBC = negative blood culture, PBC = positive blood culture.

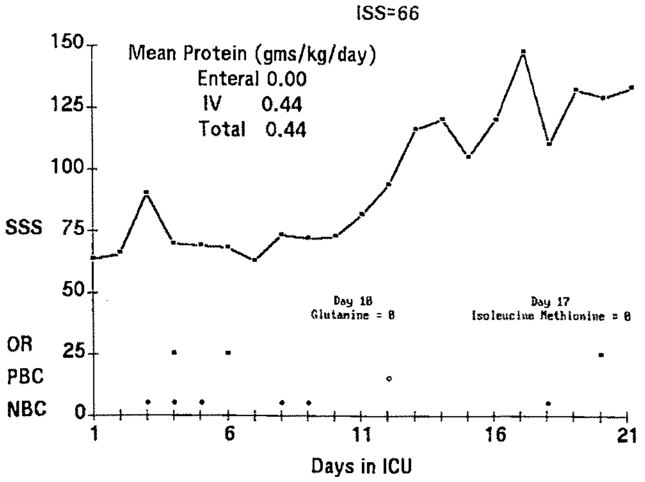

FIG. 11. The association of SSS in a patient who died of sepsis with zero EnP and very small total protein intake with splanchnic extraction. We have reported on this patient in great detail metabolically.[16,17] We therefore thought we should construct a SSS to compare with these metabolic measurements. SSS rises abruptly as glutamine extraction goes to zero on day 10 (see text for discussion) and then continues to rise as isoleucine and methionine extraction go to zero at day 17. These falling splanchnic extractions of glutamine and isoleucine are based on very low plasma concentrations produced by changes in muscle metabolism. OR = operation, NBC = negative blood culture, PBC = positive blood culture.

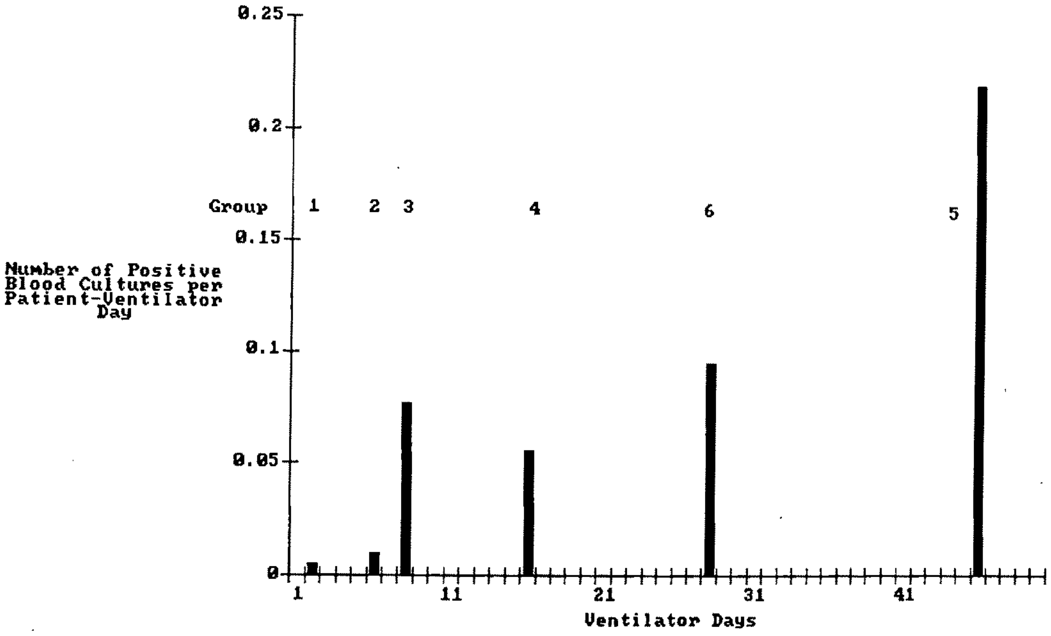

FIG. 12. The association between ventilator days and blood bacteria expressed by group as number of positive blood cultures per patient ventilator day and plotted as the group mean ventilator days. It is apparent that after 8–9 days on the ventilator the number of positive blood cultures per patient ventilator day rapidly increases and continues to increase up to ventilator day 46. The patients in group 6 died of sepsis and have the expected number of positive blood cultures for the days they spent on the ventilator as extrapolated from the surviving patients. This group is not different from the surviving patients by this measure.

Group 6 has no distinguishing bacteriologic evidence to suggest excessive infection relative to those who survived.

The most common organisms isolated from the blood of these patients were, in order of frequency: *S. epidermidis,* Candida, and Pseudomonas. These patients commonly had blood cultures positive for multiple organisms. If one bacterium was repeatedly cultured and the correct antibiotic chosen, then that bacteria commonly disappeared only to be immediately replaced by a bacterium resistant to the antibiotic used. The successful use of an antibiotic at most changed the name of the bacteria in the blood.

Table 20 lists a series of stepwise multiple linear regressions for SSS under different time conditions (0–3 days, 3–10 days, period of REI), for all surviving patients over all days, and all patients over all days. These regressions are not used as time series and do not predict SSS by day. The following independent variables are for condition: (1) Vd and EnP; (2) Vd, EnP, AB/d, (3) Vd, EnP, AB/d, and TPC, and (4) others. In days 0–3, the variables used are Vd and TCT (total cultures taken), and the adjusted R2 reaches only 0.125 and an F of 15.

TABLE 18. *Blood Cultures and the Septic Severity Score (SSS)*

	N	Septic Severity Score (Mean ± SD)
Days of positive blood cultures	107	67.4 ± 19.7*†
Days of negative blood cultures	274	62.8 ± 19.9*
Days of no positive blood culture	1536	53.6 ± 19.6†

* Statistically significant at $p < 0.04$.

† Statistically significant at $p < 0.000$.

We are unable to find satisfactory correlates of SSS in this period. This is the period when SSS falls, the groups are the same by ANOVA, and Pearson correlations show many nonsignificant correlations of SSS to its components. The correlation with SSS in this period is not improved with the use of ISS or the fluid volume given in the first 48 hours. These two variables have strong cross-correlations between themselves as might be expected.

Patients in Group 1 (Figs. 4 and 5) have all surgery done the night of admission including fractures. This group is largely synonymous with Group 1 in our earlier publication.[1] Because of total surgical care the night of admission, patients in Group 1 can sit up on the second to third day, are off the ventilator largely on that day, are spontaneously eating, and are discharged from the ICU by 7 days. Group 1 has the same ISS as the other groups. This same response occurs whenever the patients are gotten out of bed sitting up (Fig. 4) even though they are still on the ventilator (Fig. 6).

Days 3–10 for Groups 2–6 are a time of stable to rapidly rising SSS (especially Groups 5 and 6). In this period, reasonably good adjusted R2s (0.321 and 0.344) and Fs (102 and 76) for regressions in which SSS is dependent and the independent variables are AB/d and Vd or AB/d, Vd and TPC are obtained. All coefficients are positive and highly significant as opposed to zero. Adding TPC to AB/d and Vd produces only a slight rise in adjusted R2 and a considerable fall in F. TPC therefore does not add any large amount of new information to AB/d and Vd. This is a period in Group 2–6 of largely zero EnP and the enforced supine position, and, therefore, this variable is not entered.

TABLE 19. *Match of Blood Bacteria to other Sites in Groups**

	Group 1 (N = 11)	Group 2 (N = 14)	Group 3 (N = 12)	Group 4 (N = 13)	Group 5 (N = 12)	Group 6 (N = 4)	All (N = 66)
Number of patients with positive blood cultures	0	1	5	6	12	4	28
Mean number of blood cultures obtained per patient	1.5	2.6	6.6	11.0	31.0	16.0	11.0
Mean number of positive blood cultures per patient	0.0	0.1	0.8	1.9	11.0	2.2	2.6
Mean number of times blood bacteria matched bacteria cultured from other sites (±3 days) in patients with positive blood cultures	0.0	0.0	0.2	2.4	4.1	1.5	2.4

* Excluded: Candida, *S. epidermidis*, and Pseudomonas.

The time period REI is defined in Figure 5 for each group. This period varies in its beginning from Group 1 (day 3) to Groups 2, 3, and 4 (days 4–5) to Group 5 (day 11) and extends to the end of the study period for each group (day 7, Group 1; day 14, Group 2; day 21, Group 3; day 28, Group 4; and day 50, Group 5). It is this period in which the highest adjusted R2s (0.319 to 0.439) and Fs (234 to 278) are combined. The most basic relationship occurs with Vd and EnP, but the addition of AB/d and TPC clearly improves greatly the strength of the regression as judged by the change in adjusted R2 and a small decrease in F. Thus, these variables contribute new information.

This same improvement is seen when the data base derived from the whole course of all surviving patients (Groups 1–5) is used for regression. In this data base, addition of AB/d to Vd and EnP as an independent variable improves greatly the adjusted R2 (0.273 to 0.376) and F (285 to 302). Thus, AB/d includes considerable new information. The addition of TPC improves adjusted R2 (0.376 to 0.417) but decreases F (302 to 268). TPC adds some new information but not a large amount like AB/d.

The entry of all data on all patients (*i.e.*, including the deaths) causes some deterioration of the regression analysis characteristics since both adjusted R2 (0.417) to 0.366) and F (268 to 234) drop under identical conditions (Vd, AB/d, TPC, and EnP as independent variables), whereas N increases (1496 to 1611).

This problem is best examined in Group 6. Overall the regression of SSS on Vd and EnP for those four patients gives an adjusted R2 of 0.153 and an F of 11.5. AB/d and TPC when offered in this regression are not used because their coefficients are not significantly different from zero.

For Group 6, we are unable to do a satisfactory regression analysis with the variables that work fairly well for those patients who survived. One patient in the

TABLE 20. *Multiple Linear Regression: Predicting Septic Severity Score*

Condition*	Group†	Time (Days)	Sign and Step of Variable Entered 1	2	3	4	Adj R^2	SE	F	DF
2	1–6	0–3	+Vd	0	0	—	0.10	10.5	23	1/190
4	1–6	0–3	+Vd	+TCT	0	0	0.13	10.3	15	2/190
2	2–6	3–10	+ABd	+Vd	+TPC	0	0.32	12.9	102	2/428
3	2–6	3–10	+ABd	+Vd	+TPC	0	0.34	12.6	76	3/427
1	REI	All	+Vd	−EnP	—	—	0.32	15.0	278	2/1198
2	REI	All	+Vd	+ABd	−EnP	—	0.40	14.2	262	3/1187
3	REI	All	+Vd	+ABd	+TPC	−EnP	0.44	13.7	234	4/1494
1	1–5	All	+Vd	−EnP	—	—	0.27	15.2	285	2/1511
2	1–5	All	+Vd	+ABd	−EnP	—	0.38	14.0	302	3/1496
3	1–5	All	+Vd	+ABd	+TPC	−EnP	0.42	13.6	268	4/1496
1	1–6	All	+Vd	−EnP	—	—	0.29	17.5	325	2/1628
2	1–6	All	+Vd	+ABd	−EnP	—	0.34	16.9	276	3/1613
3	1–6	All	+Vd	+ABd	+TPC	−EnP	0.37	16.5	234	4/1611

* Condition: 1 = Vd, EnP; 2 = Vd, EnP; ABd; 3 = Vd, EnP, ABd, TPC; 4 = others.

† REI Group 1 Days 3–7, Group 2 Days 5–14, Group 3 Days 6–21, Group 4 Days 5–28, Group 5 Days 11–50.

Vd = Ventilator days.
ABd = Antibiotics/day.
EnP = Enteral protein (g/kg).
TPC = Total positive cultures.

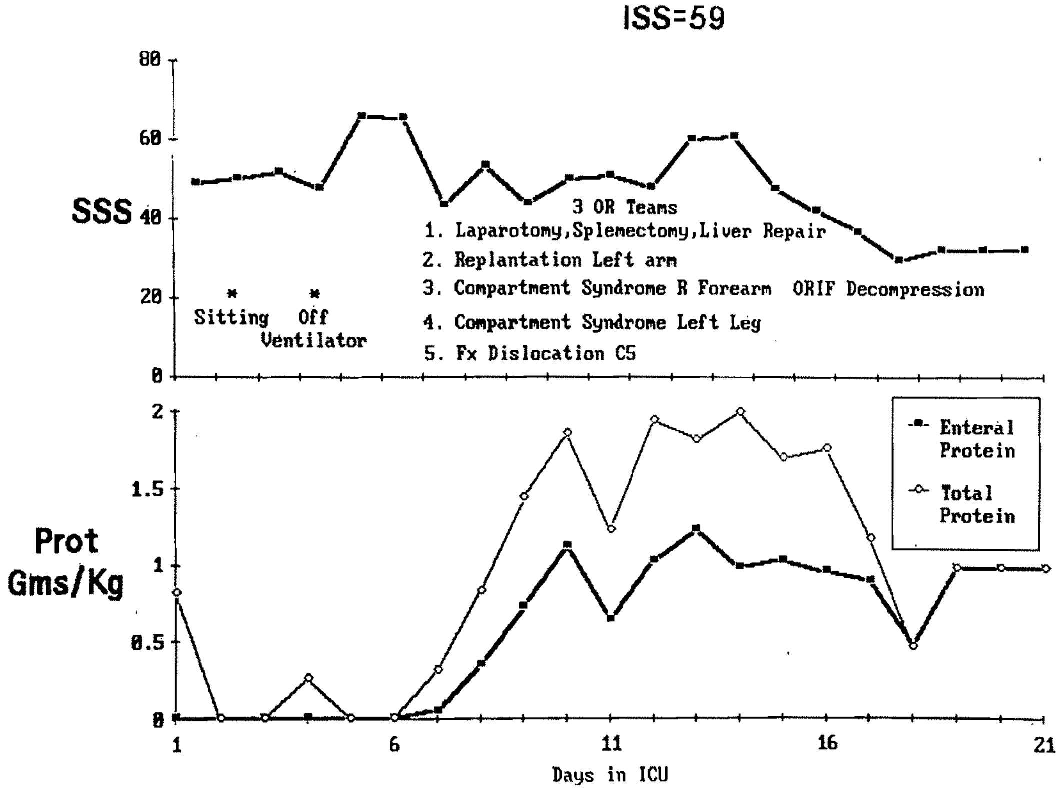

FIG. 13. The effects of initial total operative care followed by getting the patient out of bed and sitting up the next day on SSS, EnP, and IVP. This patient had severe life-threatening injuries and was left in shock with inadequate fluids for about 2 hours before being transferred to our hospital. He was an ideal candidate for the prolonged pulmonary failure septic state and perhaps death. Oxygen transport was vigorously restored and maintained throughout the operation. Three operating teams worked simultaneously in the first shift and two in the second shift. At the conclusion of the surgery, the patient could sit up out of bed the next day. He was off the ventilator on days 3–4 and had increasing EnP on day 6. His ICU course was short and without incident. This objective can be repeatedly achieved if simultaneous operating teams are used the first night.[1,10,14]

group had a different time course for SSS than the other patients (cf. Figs. 10 and 11). Excluding this patient did not improve our regression analysis. The dominant observations in this group are the lack of enteral protein intake and the lack of any bacteriologic differentiation from those who were in the ICU on the ventilator a comparable period.

The essential point of the regression analysis is that the variables found to be important individually in Pearson correlations are found to be important as an organized body of overall information by regression analysis. This analysis confirms the signs of variables previously found and shows that AB/d is again entered as a positive coefficient for SSS and not as the negative coefficient we would expect if the antibiotics were doing the job we desire. This analysis shows that increased numbers of antibiotics per day are associated with the patient getting worse.

Figure 13 shows the course of a severely injured young man (ISS = 59) who was initially taken to another hospital where he was allowed to be in moderate to severe shock for about 2 hours. He had a ruptured spleen and liver, amputation of the left arm above the elbow, a fracture of C5 with subluxation, a severe head injury, a comminuted fracture of the right forearm with a compartment syndrome that limited circulation to the right hand, and a compartment syndrome of the left leg without fracture that limited circulation to the foot. Oxygen transport resuscitation was achieved rapidly and the patient was operated on with oxygen tensions in the 150–200 mmHg range and urine outputs above 150 mL/h. The cervical spine was immobilized by traction. Three operating teams were employed: one for the abdomen, one for the left arm replantation, and one for the right arm decompression with open reduction and internal fixation of the fractures. The left leg was done after the abdomen and at the same time a halo vest was applied. With this management, the patient was sitting up and out of bed the day after his injury, he was off the ventilator at 4 days, and began enteral intake at day 7. The increase in SSS after weaning probably means he was weaned from the ventilator a day or two early. He was kept in the ICU for days 10–17 primarily to observe the circulation in his arm. On days 13 and 14 he had a septic response for which no bacteriologic site was ever found. This case illustrates management of night of admission that prevents the prolonged pulmonary failure septic state and the subsequent gut origin septic states we have been discussing. This objective can be achieved reproducibly as we have previously shown.[1]

Figure 14 shows the duration of stay of the individual patients in the ICU. The individual time varied from 3 to 135 days to form a logarithmically decreasing curve. It also shows the regression equation that best predicts TICUd based on the individual patient characteristics. The independent values that best predict the curve are

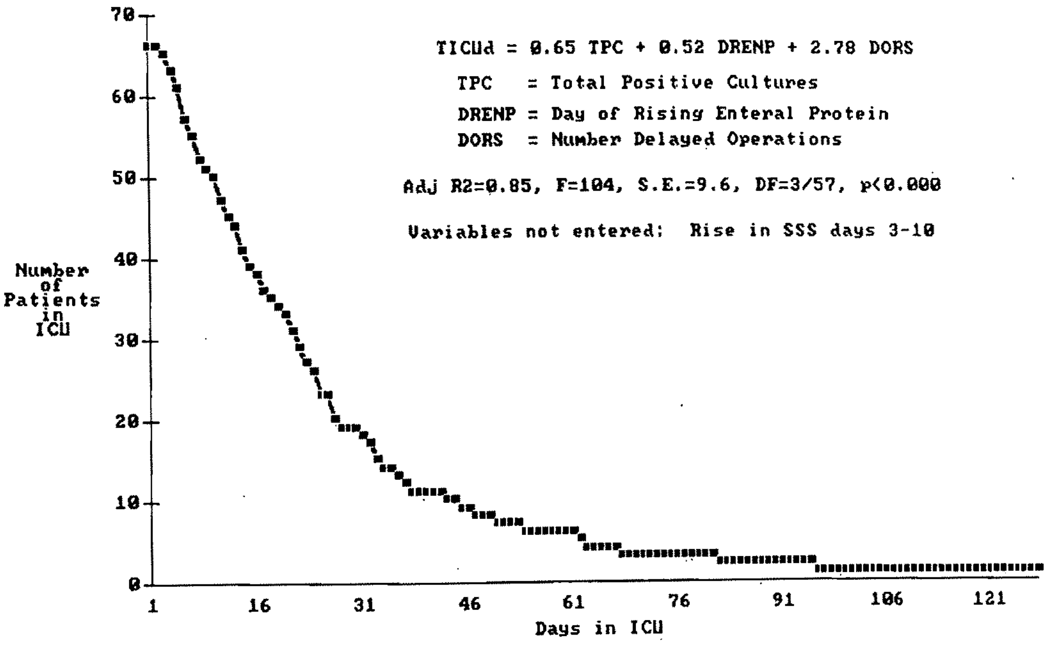

FIG. 14. A plot of ICU days and number of patients in the ICU each day shows a logarithmically decreasing curve. Total ICU days is best predicted with the independent variables: number of delayed operations (DORS), day of rising enteral protein (DREnP), and total positive cultures (TPC) (adj. R sq. = 0.84, F = 104, dF = 3/59). The variable of greatest importance is DORS and the next greatest is DREnP. TPC is highly correlated with both of these variables but does contain some new information.

number of delayed operations, TPC, and day of REI defined as the day it exceeded 0.3 g. Adjusted R2 is high at 0.85, whereas F at 104 is reasonable for the degrees of freedom. This regression is of extreme importance. All previous statistical comparisons have been based on the arbitrarily chosen groups and have been for intensive or daily variables. This analysis is based on individual patient characteristics and is for extensive variables. It therefore has an entirely different basis. The fact that it is using largely the same variables confirms the importance of the associations previously observed. Incomplete operative care the night of admission seen here as number of delayed operations is of dominant importance for the duration of stay in the ICU (TICUd). We have previously shown that TICUd is tightly correlated with TVd (Pearson r = 0.92, $p < 0.001$, N = 62) and that the bacteriologic evidence of infection is tightly correlated with TVd after day 9. In figures 1, 2, and 3 we show the effect of no enteral protein, traction, and three or more delayed operations on SSS and EnP. The effects are also shown in Tables 10, 11, 12, 13, 14, and 15. The essential point is that delayed operations of all kinds (not just fractures) are associated tightly with prolonged ventilator support and reduced enteral protein (see discussion for consideration of emergency operation). If these factors prolong ventilator support and reduced enteral protein beyond day 9, then bacteriologic evidence of infection and the gut origin septic states develop.

Discussion

We would suggest that the primary determinant of the magnitude of the septic state and the duration of stay in the ICU is incomplete surgical care the night of admission. We would further suggest that incomplete surgical care the night of admission leads to greater use of analgesics, prolonged use of broad-spectrum antibiotics and other drugs, intravenous lines, monitoring and drainage lines, ventilator lines, and patient care that produces the enforced supine position. Traction for fractures is only one method of producing the enforced supine position.[1] Secondary to the enforced supine position in the patient with multiple trauma, the viscera presses continuously against the diaphragm to produce a failure to deep breathe and therefore cough with resultant atelectasis and retained secretions. These activate the pulmonary alveolar macrophage to produce the septic state. In addition, the same position causes high capillary hydrostatic pressure and blood flow in the posterior dependent lung, which is not as accustomed to this as are the bases of the lungs. Concurrently, there is excessive escape of wound destructive processes such as complement split products, lysosomal destructive enzymes, procoagulant factors, oxygen free radicals, prostaglandin E (PGE2), and leukotrienes and escape of normally released products such as the interleukins. These are all macrophage products and their release begins after macrophage maturation and activation. This occurs about days 3–4 and accounts for the stable to falling SSS from days 0–3.

The excessive escape of wound destructive processes produces, when combined with the enforced supine position and its effect on pulmonary blood flow, damage to pulmonary tissue to enhance the pulmonary failure and to further activate the pulmonary alveolar macrophage.

The combined release of wound and pulmonary macrophage interleukins then accentuates the systemic septic state. This effect may be enhanced by entry of gut endotoxin to the systemic body to activate the hepatic macrophages. The excessive escape of wound destructive processes not only makes the pulmonary failure worse but also suppresses the immune system and the function of the polymorphonuclear cell. For the polymorphonuclear cell, this occurs by excessive escape of complement split products so that the cell is desensitized to a second exposure and thus has a reduction in all its functions.

The Lung, the Wound, and the Subsequent Bacteriologic Evidence of Infection

PGE2 in the wound normally suppresses immune function by inhibiting production of interleukin 2 (IL2) and therefore generation of T-helper inducer cells.[2,3] With a normal lung, all PGE2 is cleared from pulmonary artery blood by the lung so that none enters the systemic body.[4] This allows locally generated PGE2 to be utilized widely in the systemic body as a microregulator of metabolism and function. The existence of major wounds and macrophage activation greatly increases the load of PGE2 presented to the lung. The enforced supine position and its associated pulmonary failure probably reduces the capacity of the lung to clear PGE2. In addition, pulmonary damage produced by a variety of mechanisms plus the embolic material presented to the lung (activated aggregates of white cells and platelets, fat emboli) under these conditions all activate the pulmonary alveolar macrophage. This macrophage then becomes a source of PGE2. We speculate these combined events allow PGE2 to enter the systemic body to suppress T-cell mediated immunity generally and the secretory IgA system of the mucous membranes specifically.[2,3] This effect plus the absence of enteral food intake and the effect of prolonged broad-spectrum antibiotics on the commensal bacteria then produce the tight association between ventilator days and the bacteriologic evidence of infection if they last beyond 10 days.[5-9]

Normal Function of the Upper Airway, Oropharyngeal, and Upper Gut Antibacterial Systems

The secretory IgA system is of dominant importance for the oropharynx, the airways of the lung, and the gut. Secretory IgA after synthesis is delivered directly to the surface of the mucous membranes in mucus, *via* salivary gland secretions for the oropharynx, and *via* biliary tract secretions for the upper gut. Secretory IgA does not kill bacteria but rather binds to them and thus prevents binding of the bacteria to cells of the mucous surface. It works in conjunction with the commensal bacteria of the gut, which bind to cells of the mucous membrane where they consume nutrients and release metabolites toxic to many pathogenic bacteria. These metabolites operate in the oropharynx in conjunction with lysozyme, another product of the salivary gland.

The bacteriocidal mechanism of the upper gut, oropharynx, and airways is stomach digestion of bacteria and the secretory IgA bacterial complex. This depends on the ciliary ladder of the airways to deliver mucus to the pharynx and the physical movement of saliva from its point of secretion to the pharynx. This combined material is then swallowed for stomach digestion. The dominant factor that causes the whole system to operate properly is food ingestion. This stimulates secretion of the salivary glands, liver, and stomach while physically cleaning the oropharynx and esophagus and locally supporting growth of the commensal bacteria. Food ingestion at the same time specifically stimulates growth and replication of the enterocytes, secretion of mucus, the gut associated lymphoid tissue and immune system, the secretion of bile salts to neutralize endotoxin, and subsequently, defecation to reduce the penetration of bacteria and endotoxin in the colon. As a result of these functions, the upper gut below the oropharynx is largely sterile and the barrier function of the mucosa is well maintained.

Origin of the Bacteriologic Phase of the Septic Response

Largely due to the enforced supine position, these patients remain in pulmonary failure requiring intubation and ventilatory support with all of its associated management and become more septic or at least remain the same. In response to these problems, they receive a large number of medications that keep them lethargic. They remain in the enforced supine position (horizontal crucifixion position) because of this and the many lines for support, monitoring, drainage, and the need for delayed planned operations. These medications may also inhibit salivary, biliary, and gastric secretions. At the same time, the stomachs of these patients are alkalinized to prevent stress ulcers. Because the patients are septic, they receive prolonged broad-spectrum antibiotics that kill the commensal bacteria and help the gut to evolve antibiotic-resistant bacteria. The endotracheal tube and the medications largely prevent enteral food intake, while also preventing movement of the mucus of the airways into the pharynx and maintaining a partially open mouth so that the oropharynx dries out. The endotracheal tube provides a pathway for bacteria from the oropharynx to the airway of the lungs.

In addition, these patients have a generalized suppression of T-cell mediated immunity with a speculated suppression of the secretory IgA system, and a PGE2 systemically altered metabolism.[2,3] While these are occurring, the absence of food intake progressively decreases the function of the gut mucosa as a barrier, while the enforced supine position augments the gastric and colonic stasis of the basic ileus. This provides more time for bacterial growth and penetration in the stomach and inhibits defecation to maintain a high colonic penetration pressure for endotoxin and bacteria.

Death from sepsis does not occur from the bacteria unless they produce destruction of the lung (?pneumonia) that prevents oxygen transport (two patients). The bacteria are merely markers of advanced organ failure generally but especially of the gut mucosa. All patients who died of sepsis had no enteral protein intake or a prolonged period of no enteral protein intake and were in the enforced supine position. Death from sepsis probably occurs from entry of gut endotoxin into the body to damage the function of all organs. It is probably also true that the hepatic damage that occurs reduces bile salt secretion to detoxify endotoxin so that the endotoxin in the gut is more toxic.

The essential point is that the treatment of the pulmonary failure septic state of the first 10 days in an inappropriate way based partly on an assumption of a bacterial origin directly inhibits practically every aspect of function of the normal antibacterial system of the oropharynx, airways, and upper gut. Secondary to this, the gut origin bacteriologic septic states begin around 10 days of critical illness with ventilator support. After this, the problem becomes increasingly one of bacteriologic sepsis due to the antibiotic-resistant bacteria generated in the first 10 days.

Van Saene et al. from Groningen have defined the normal commensal bacteria of the gut.[8] They showed that with increasing days of ventilatory support with conventional prolonged broad-spectrum antibiotic use in the trauma patient, this flora becomes increasingly pathogenic and antibiotic resistant. The oropharyngeal flora was then found in the upper airways and stomach and finally in the blood, pneumonia, urinary tract, and wounds.[9] They then tried to define a group of antibiotics that were active against pathogenic bacteria and largely commensal bacteria neutral. They used these antibiotics to selective decontaminate the gut with special emphasis on the oropharynx. They showed with their approach but with historic controls a considerable reduction in infection (80% to 15%) and mortality (5 of 47 to 0 of 51).[6,7] Marshall et al. from Montreal have reported a very high mortality in association with the same antibiotic-resistant bacteria in infections in patients in the ICU and the appearance of the same bacteria in the stomach.[5]

This hypothesized course best explains the positive correlation and coefficients obtained for SSS that are strongest and most positive for ventilator days, next for antibiotics per day, and weakest for total positive cultures. The same rationale explains the strong negative correlations and coefficients for EnP that strongly supports all of the normal antibacterial mechanisms of the oropharynx, airways, and upper gut and encourages defecation for the lower gut. These same concepts clearly apply to the duration of stay in the ICU correlations and coefficients where the independent variable of greatest importance is the number of delayed operations, which is positive. The variable of next greatest importance is a rise in enteral protein intake above 0.3 g protein/kg/day.

The data presented here are completely consistent with preceding data on this topic. Thus, the entire blunt multiple trauma fracture literature states unanimously that conservative management with femoral traction of fractures of the femur, acetabulum, and weight-bearing pelvis relative to immediate operative management is associated with a considerable increase in the magnitude and duration of the pulmonary failure septic state that follows blunt multiple trauma and in the number of late septic deaths.[1,10–14,33] These same data also show the increased bacteriologic phase beginning at 10 days.[1] These are probably all gut origin septic state deaths and bacteremias. The duration of the pulmonary failure septic state in our previous work had no statistical relationship to the magnitude of the original injury as judged by the Hospital Trauma Index–Injury Severity Score (HTI–ISS) but was tightly associated by every criterion with the days of femoral traction.[1] Despite the fact that HTI–ISS should reflect the total magnitude of devitalized tissue present, we had chosen to interpret the pulmonary failure septic state as resulting from the action of the macrophage on fracture hematoma and devitalized tissue since this was resected with our open internal fixations.[1]

This is no longer a feasible interpretation. Thus, femur fractures may be internally fixed open (resection of hematomas and devitalized tissue) as we did or closed (hematoma and devitalized tissue left in place) as Bone et al. did in their prospective randomized study.[1,10] Both techniques result in the same beneficial effect in terms of reducing the duration and magnitude of the pulmonary failure septic state, and both allow the patient to be out of traction so that he can sit up relatively pain free a day or two after injury. We must therefore conclude that in the patient with blunt multiple trauma, the enforced supine position produced by traction by itself increases the magnitude and duration of the pulmonary failure septic state. This is also consistent with no relation of HTI–ISS to the magnitude and duration of the pulmonary failure septic state.

This is an important conclusion since the patient may be in the enforced supine position (horizontal crucifixion position) for many other reasons, such as the medications required to keep the endotracheal tube in place, the need for several delayed planned operations, and the multiple lines required for intravenous support, monitoring, drainage, and ventilatory support. This problem is well illustrated by our data on traction, delayed operations, and no enteral protein support in addition to the correlations with three or more delayed operations. It is this particular factor that makes days on the ventilator such an important variable.

The data on EnP fits exactly into our previous work,[15-17] the work of Clowes and associates,[18-21] the work of Alexander and associates,[22-24] the work of Antonacci et al.,[25] and some work of Wilmore and Souba.[26-28]

Wilmore and colleagues demonstrated that at least from the vascular side, the gut uses little glucose for energy and consumes predominantly ketone bodies and glutamine.[27,28] The septic response largely shuts off ketogenesis leaving the predominant fuel of the gut as glutamine.[15,29,30] We have shown in this paper that the patient we studied and reported on in great detail much earlier became much more septic as the gut plus liver glutamine extraction went to zero and then continued to get much more septic as the extraction of isoleucine and methionine went to zero. Our previous paper showed that these changes were secondary to a very low concentration of glutamine and isoleucine.[16,17] Glutamine is unstable and is not contained in intravenous amino acids. The patient receiving intravenous hyperalimentation uses muscle to convert valine to glutamine to support the enterocyte. One of the markers of impending death from sepsis is that the plasma valine concentration rises and valine begins to behave as an hepatic catabolized amino acid.[29,31] That observation is the counterpart of the low glutamine and zero glutamine extraction shown here and elsewhere. The infusion of glutaminase causes glutamine to go to zero in the experimental animal with the development of multiple gut mucosa lesions and death of the animal.[27] Hwang et al. have shown that addition of glutamine to conventional amino acids in experimental animals is associated with a thicker gut mucosa.[26] Thus, glutamine is clearly of considerable importance as a fuel to support the enterocyte. Ingested intact protein contains glutamine since it is stable under these correlations but more importantly contains a large number of amino acids that can easily be converted to glutamine.

Clowes and colleagues have shown in a number of papers that reduced central plasma clearance of amino acids is a marker of impending death in the septic patient.[18-21] Technically, central plasma clearance includes amino acid extraction by all organs other than muscle. It is clearly increased by intravenous amino acid infusion at the same time muscle amino acid release is reduced.[18] Those patients who eventually die have a much smaller increase in central plasma clearance when amino acids are infused than those who survive.[21] Practically, the dominant organs measured by central plasma amino acid clearance are clearly the gut and liver. These observations are entirely consistent with our observations but both are made on intravenous support.

Alexander and associates showed in a prospective randomized trial that in severely burned children an increase in enteral protein intake of 25–50% relative to recommended intake was associated with a considerable reduction in mortality rate, septic behavior as judged by antibiotic days, and the use of red cells and plasma.[22] They then showed in burned guinea pigs that enteral protein intake relative to intravenous, begun within hours of the burn, produced a much thicker gut mucosa in association with largely shutting off the septic neuroendocrine response.[24] Subsequently, they showed that intact protein was much more effective than an equivalent amino acid mixture.[23,32] Antonacci et al. repeated Alexander's prospective randomized study in severely burned adults and made the same observations of reduced mortality rate despite more severe burns in the high protein group. They also observed that nitrogen balance was not improved, whereas several aspects of immune function were greatly improved.[25]

All of this literature is entirely consistent with our observations of a very special effect of enteral protein in reducing the magnitude of the septic state and the bacteriologic evidence of the septic state in a way that cannot be achieved with intravenous protein or amino acids no matter how much is given. It is probably true that high intravenous amino acids are important in allowing survival while extreme septic states persist.[15] This is probably a direct cause of our high survival rate. That is an entirely different issue from reducing the magnitude of the septic state and its bacteriologic evidence. The evidence presented here and the background on which it is presented seems to show rather clearly that the conventional prolonged use of multiple broad-spectrum antibiotics does not benefit these patients and that it almost undoubtedly directly contributes to the gut origin septic states that lead to death.[6-9] Short-term selective antibiotics for specific problems probably have considerable beneficial effects. We have not investigated that problem. Finally, it seems equally clear from these data and those of others that the traditional surgical incomplete operative management the night of admission with its traditional associated ICU care and delayed operations (horizontal crucifixion position), directly contributes to and probably produces the prolonged pulmonary failure septic state that produces the antibiotic management that later produces the gut origin septic states.[1-13,33]

These combined events probably result in many of the emergency operations these patients require, which are probably direct products of their gut origin septic states (*e.g.*, tracheostomy, subphrenic abscess, wound infections, laparotomies to search for abscess, sinus abscesses, parotitis, prostatic abscesses). We have demonstrated rather clearly in our preceding paper that this whole complex can be avoided by total surgical care including fractures the night of admission followed by getting the patient out of bed, sitting up, and off the ventilator a day or two later.[1] The data presented here support that paper but point out that the same effect occurs with all delayed surgery, femur tractions simply being the most obvious and perhaps most potent example.

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DISCUSSION

DR. MARTIN ALLGÖWER (Basel, Switzerland): Thank you for the privilege of discussing this most stimulating paper. I may point out a few things that support what Dr. Border said.

Since 1958, for us, fractures have been an emergency, particularly in multiply injured patients. It so happens that in 250 multiply injured patients by a combination of this aggressive total care to the body cavities along with the fractures of the long bones and with adequate ventilation under PEEP, the so-called fat embolism syndrome has practically disappeared and looks like a ghost of the past.

One day in Switzerland we had a surgical meeting where two neighboring cities presented their results with about the same number of multiply injured patients. Our neighbor city was complaining of a series of fatal fat embolism, whereas none occurred in our patient series.

We put our results together, submitted them to the *Journal of Trauma,* but it was not a prospective study and, therefore, it was turned down. We were so convinced of our approach that we did not ethically feel justified to make a prospective study.

I believe it is most noteworthy that we owe to John Border the insight that many so-called sequellae of trauma are related to treatment modalities rather than to the trauma as such. Studying the alveoloarterial O_2 difference in two patient groups, one in prolonged supine position with their fractures in traction, the other with the immediate total care, including operative fixation of long bone fractures, one finds the alveoloarterial O_2 difference normalized within 3 days in the aggressively treated group. The conservatively treated group needs 10 days on the average and does not even completely normalize its pulmonary physiology, demonstrating that prolongation of this pulmonary insufficiency is clearly treatment related.

One thing that was quite impressive to us was that at entrance to the hospital, the circulatory state seems to be of some prognostic importance. It may be appreciated by looking at the quotient of pulse rate over blood pressure, a value that we have proudly called "shock index." The impending danger appears at a value of 1 and becomes life threatening at 1.5. Evidence was supported by two groups of clinical findings. In 25 septic patients of a group of 250 multitrauma patients, the patients who were going to die had at entry to the hospital a shock index of 1.58 ± 0.52, whereas those who survived entered the hospital with a mean shock index of 1.17 ± 0.2. The same observation was true for a group of 84 patients with ruptured spleens in combination with other injuries. Those with a shock index of over 1 at entry to the hospital had twice the mortality rate of the group with a shock index below 1.

This simple and rather primitive parameter is valid only in the recently traumatized but seems to indicate that very early on some homeostatic mechanisms, even in reversible shock, get damaged. It would appear interesting to get more data concerning the simple parameter to evaluate recently traumatized patients. Incidentally, looking at this shock index in the four groups of patients recently published by Border, it completely agreed with his evaluation of the severity of injury.

Two questions to Dr. Border would interest me. We certainly should remember Jacob Fine who was pointing out clearly that susceptibility to any toxin, but particularly to endotoxin, is much increased even after a reversible shock episode. Is this mechanism instrumental in Dr. Border's observations?

The second question is how do you determine at what moment the ventilator becomes a hazard, or rather, how do you avoid it?

DR. GEORGE H. A. CLOWES, JR. (Boston, Massachusetts): Dr. Border kindly provided me with an up-to-date copy of his paper, which I believe will nicely supplement this talk.

The point I want to make is what Dr. Border has done for us. He has documented that the sicker the patient is, the worse his overall problem, and if his illness is substantially prolonged, he will die with probable overwhelming infection in what we term "multisystem failure."

I would like to point out that the basis for all this is what Dr. Border has partially pointed out, namely, protein synthesis. The immune system, as Wesley Alexander and others have clearly shown, does not work without protein metabolism going on. I presented data to this society 2 years ago in which we showed that people who died in multisystem failure with overwhelming infection did not respond to uptake of amino acids in their visceral tissues. The liver protein metabolism correlates with the amino acid uptake.

More recently, Dr. Bosari in our laboratory has conducted some experiments in which he showed that the protein synthetic rate in the small bowel increases significantly 24 hours after the onset of experimental infection.

Dr. Border has emphasized the need for the enteric nutrition, but if you look at his graphs, you will see that those people who were critically ill with abdominal problems, and consequently could not take enteric nutrition, also developed pulmonary complications and finally died. This is further documentation, although not definite, pointing to the gut as the origin of this infection that kills people.

The other point I want to emphasize is that the sooner we can begin administering enteric nutrition, such as in severely injured patients at risk of dying whom Dr. Border and I see at our respective hospitals, the better their chance for survival. This is evidenced by the fact that Dr. Border had only four deaths in 66 seriously injured patients, which says that he is doing something right.

I look forward to studying this manuscript in greater detail. It is a fine follow-up to what Dr. Carrico, Dr. Meakins, and others did recently in a symposium on multisystem failure where protein synthesis and pulmonary failure were emphasized.

DR. JOHN F. BURKE (Boston, Massachusetts): I rise to congratulate Dr. Border on the collection of a large and accurately compiled data base followed by an intensive statistical analysis of the data.

This area is important, and I believe the points made are of value to the management of massive injuries.

I have two questions. First, the evidence is, I believe convincing, that bacterial invasion at least in the early phases of recovery from injury are not a prominent cause of what you have called the septic state. If this state is not caused by bacteria, what mechanisms and what initiators of these mechanisms do you postulate cause this septic state?

Second, renal failure was conspicuously absent from all of your data. In your experience, is this because you have only looked at the patients who survived and not those who died, or is this related, at least partially, to the patients' age. Your patients were very young as the spectrum goes.

DR. J. WESLEY ALEXANDER (Cincinnati, Ohio): Dr. Border has given us a very complex analysis of a very complex problem.

He has brought into clear focus the fact that despite its relatively noxious content, we should no longer ignore the critical role of the intestine as a barrier. Nutrition has long been believed to be an important determinant for resistance to infection, but specific nutritional support of the intestine has been studied only recently.

(Slide) In a burned animal model, lack of enteral nutrition for only 24 hours can result in a 50% reduction in the jejunal mucosal mass, but this loss can be prevented by immediate feeding by the enteral route, although (Slide) not by the parenteral route. (Slide) Furthermore, intact protein in the diet prevents loss of mucosal mass better than crystalline amino acids of the same composition and amount as the intact protein.

In our studies with burned patients, there has consistently been a direct relationship between the amount of intravenous nutrition that the patients receive and the incidence of sepsis. (Slide) These studies and others have led us to the conclusion that both the septic state and hypermetabolism occur at least in part from a failure of the gut mucosal barrier and that the failure can be prevented by aggressive enteral nutrition with high protein diets, which is what Dr. Border is trying to show us.

I would like to ask Dr. Border three relevant questions. First, have you measured endotoxin levels in any of your patients, and is there a relationship to the septic severity score, or the amount of enteral protein given the patient? Second, is there a relationship between the septic severity score and the central nutritional proteins such as retinal binding protein, prealbumin, and transferrin, which in other studies have a close relationship to the development of sepsis? Third, in the patients studied, did it make any difference if the enteral protein was given as intact protein or as an amino acid solution?

DR. BENJAMIN F. RUSH, JR. (Newark, New Jersey): I simply cannot resist joining this symposium concerning Dr. Border's paper. I certainly congratulate him and his colleagues on a stimulating work and some controversial hypotheses.

John was kind enough to allow me to review the manuscript, and my first thought is that the flood of data derived from the daily management of patients in the intensive care unit is obviously overwhelming. This paper is an impressive example of number crunching in which a quarter of a billion bytes of data have been massaged to obtain meaningful correlations.

The most consistent finding is the correlation of an enteral protein diet with a decrease or absence of sepsis. Almost all other major parameters including parenteral protein without initial protein intake correlate positively with increased sepsis, with primarily enteral bacteria appearing in the blood in increasing numbers.

I have a comment and a question concerning this paper. The comment relates to our own work in a rat model of treated hemorrhagic shock.

In previous papers we have shown that if severe hemorrhagic shock in rats is treated vigorously, as we would treat shock in humans, that almost all animals survive the first hours or days of shock, but death occurs mainly in the second or third day, and if the rat survives past the third or fourth day, recovery seems complete. Death in these rats seems to correlate with the findings of positive blood cultures.

(Slide) Primarily, these cultures are of enteral bacteria. What we did in these animals was to tag some *Escherichia coli* with C-14 oleic acid and feed the animals on the C-14 radioactive compound. These are the radioactivity levels in shocked animals out to the third day. This is the radioactivity seen in unshocked controls.

(Slide) The interesting fact is that in 14 shocked animals, we had about a 50% survival rate. Of those animals who showed no radioactivity, only one animal died in the course of the 7-day follow-up. The mortality rate was 100% in those animals that showed radioactivity.

In most of these animals we were able to demonstrate positive cultures showing *E. coli* and other enteral bacteria.

Our conclusion from this was that the appearance of bacteria in the shocked animal is a very early event and that the source for the bacteria seemed to be almost certainly the gastrointestinal tract as demonstrated by the appearance of tagged bacteria from the gastrointestinal tract. That would, of course, fit with some of the comments made earlier by Dr. Allgower.

A question to Dr. Border is: how can he clearly eliminate the possibility that the ability to accept enteral feeding is not itself an index of the stronger, more resistant patient? Perhaps this question would best be answered by a prospective, randomized trial.

DR. ROBERT F. WILSON (Detroit, Michigan): I have a number of questions. What was the relationship between injury to the gut or brain and their effects on these data? Certainly if the gut is inovlved and you cannot use it for feeding for some time, this is going to change the results, and, obviously, head injury will also tend to make the outcome worse.

If, indeed, you can use the gut, it is certainly better than intravenous feeding. Is there any difference in the types of enteral feeding (gastrostomy *vs.* jejunostomy) that you should use and is there any optimal formula for enteral feeding?

Very often our sickest patients are those most apt to have negative blood cultures (because of fungi or viruses?) and get progressively more antibiotic-resistant organisms. Was there any particular relationship between the antibiotics used and the incidence of negative blood cultures and the types of antibiotic resistance?

Most people have found that there is a correlation between mortality rate and whether the initial empiric antibiotics were appropriate when the culture results eventually came back. Did that not pertain here?

Almost all of these critically ill patients with prolonged stays in the intensive care unit will have some degree of pneumonia at autopsy. Consequently, there is some question as to whether a persistent septic state without pus is due to pneumonia or a "gut septic state." I am not sure that the data presented here indicate that if the gut happens to be able to take nutrition, the gut is not the cause of the septic state. How did you determine that the gut could not be used; was it the amount of distension, nasogastric damage, or what? Most people agree that if you can use the gut for feeding, it should be used as much as possible.

We wonder what sort of attempt there will be to randomize the use of enteral nutrition to prove this particular point.

DR. JOSEPH M. CIVETTA (Miami, Florida): I have just three clarifications to ask from Dr. Border.

One, what is the definition of the gut septic state, and how is the diagnosis substantiated?

Second, what were the selection criteria used to choose between enteral or parenteral nutrition?

Third, I noted that there were four patients who died in septic states. Does that mean that the other 62 patients in the study were long-term survivors?

DR. JOHN R. BORDER (Closing discussion): We have established an objective septic severity score based on the 16 measurements made every day in the intensive care unit. This septic severity score works almost exactly as the experienced clinician does when evaluating the septic state. The statistical correlations in this retrospective study with the septic severity score are negative only for enteral protein intake and positive for all other therapeutic modalities including antibiotics. Thus, only an increase in enteral protein intake was associated with a reduced magnitude of the septic state. This statistical relationship existed at all times and under all conditions examined. When one reviews the previous literature on humans and the normal antibacterial antiendotoxin mechanisms of the gut, this relationship of increased enteral protein to a reduced magnitude of the septic state and clearance of bacteria from the blood makes good biological sense. There are now a large number of investigators who see the gut as a primary source of bacteria and endotoxin to the systemic body in chronically critically ill patients. We believe that this is largely a product of patient management. We have discussed this at some length in the primary paper.

Dr. Allgower wanted to know about the shock index. We did not calculate that variable. However, in principle, prolonged severe shock with subsequent resuscitation should lead to oxygen-free radical damage to the gut mucosa and liver and a much earlier onset of the gut origin septic states. This is in keeping with Jacob Fines' work and with Ben Rushes' work in terms of the effect of shock on the entry of endotoxin and bacteria into the systemic body.

Dr. Allgower also asked about weaning from the ventilator. The entire blunt multiple trauma literature is very consistent in that operative stabilization of fractures of the femur, acetabulum, and posterior pelvis the day of admission by allowing the patient to sit up relatively pain free shuts off the pulmonary failure septic state at 2–4 days. In contrast, femur traction produces a pulmonary failure septic state that lasts as long as the traction and which beginning at about 10 days gets rapidly worse. It is to be pointed out that our data show that femur traction is associated with a reduced enteral protein intake and a progressive increase in the magnitude of the septic state. This is also true of any kind of delayed operative therapy. We must deduce that the sitting position obtained by complete operative care the night of admission aids not only in the function of the lungs but also in the function of the gut probably in terms of both food intake and defecation.

Dr. Clowes used the words overwhelming infection. I do not agree with that because there should be bacteriologic evidence which we did not find. I believe he means overwhelming septic response. I agree with that but must point out that the septic response is a product of macrophage activation and that such activation may come from devitalized tissue as well as bacteria. Both Dr. Clowes and ourselves have shown that reduced amino acid extraction by the gut plus liver is a predictor of a septic death. Dr. Clowes' work on central plasma clearance fits exactly with our work. I wonder if the reduced gut plus liver extraction of amino acids reflects a greatly reduced mass of gut enterocytes. I would therefore speculate that perhaps enteral protein feeding could restore central plasma clearance of amino acids to normal.

Dr. Burke's question is based on nonbacterial causes of the septic state. It is clear from cell biology that any factor that activates the macrophage can produce release of the factors that produce the septic state. The factors that activate the macrophage are endotoxin (especially the hepatic macrophage) and phagocytosis of any material from latex beads, to colloidal gold, to devitalized tissue, to bacteria. I believe these patients were initially septic from phagocytosis of devitalized tissue secondary to wounds and the effect of the enforced supine position on the lung. Our treatment of this septic state with the ventilator and intubation, no food intake, alkalinization of the stomach, and broad-spectrum antibiotics then created by days 8–10 a bacterial endotoxin septic state with pathogenic antibiotic-resistant bacteria. The bacterial phase of this problem (and presumably the endoxin phase) then gets progressively worse from days 8–10 to at least day 28 when all patients are involved with multiple positive blood cultures. It is my opinion that aggressive protein support (2.5 g/kg/day), although it does not treat or reverse this septic state, does allow the patient to endure and survive until enteral protein intake is increased.

It is of considerable interest to me that oliguric renal falure did not occur except for one patient in the patients who survived. That one patient came very close to death and was not supported as the other patients were. I attribute this absence of oliguric renal failure to our fluid support, which maintained an average of 3600 mL of urine output per day. I suspect strongly that many patients who die in association with oliguric renal failure actually die of protein malnutrition and the gut origin septic states.

Bob Wilson wanted to know about feeding the injured gut. There are a wealth of papers that clearly show that patients can be fed almost immediately after bowel surgery; they can be fed with peritonitis, and they can be fed immediately after major intra-abdominal trauma. We must realize that an ileus is as gastric and colonic stasis and not a jejunoileal stasis. The upright chest position helps greatly (probably) in getting liquid foods through the stomach. It also greatly aids defecation, which is equally important. Alternatively the stomach may be placed on suction and the feeding given into the upper jejunum. Only bowel obstructions and high fistulas contraindicate such early enteral feeding.

How much enteral protein is enough to prevent the gut origin septic states? Enteral protein in the amount of 0.3 g/kg/day is clearly too little, 0.6 g may be enough, but 1.0 g is probably better. We have customarily given both enteral and intravenous protein support so that in critically ill humans we achieve about 2.5 g/kg/day. It is important to note that this is only achieved with orders for 3.5–4.0 g/kg/day since everyone seems to believe they have the right to withdraw nutritional support. It is further important to note that we could find no evidence for a beneficial effect of broad-spectrum antibiotics in treating these patients and, in fact, our correlation suggest harmful effects. The most important antibiotic in this study was clearly enteral protein.

The biggest question for this whole study is clearly whether the patient has more enteral protein intake because he is getting better (self-fulfilling prophecy), or whether he gets better because he has more enteral protein intake. We would suggest since the same relationship between enteral protein and reduced septic state is seen at all times and under all conditions, since there is a large background literature, and since it is consistent with basic biology, that the patient gets better because of more enteral protein. Other observers may believe differently.

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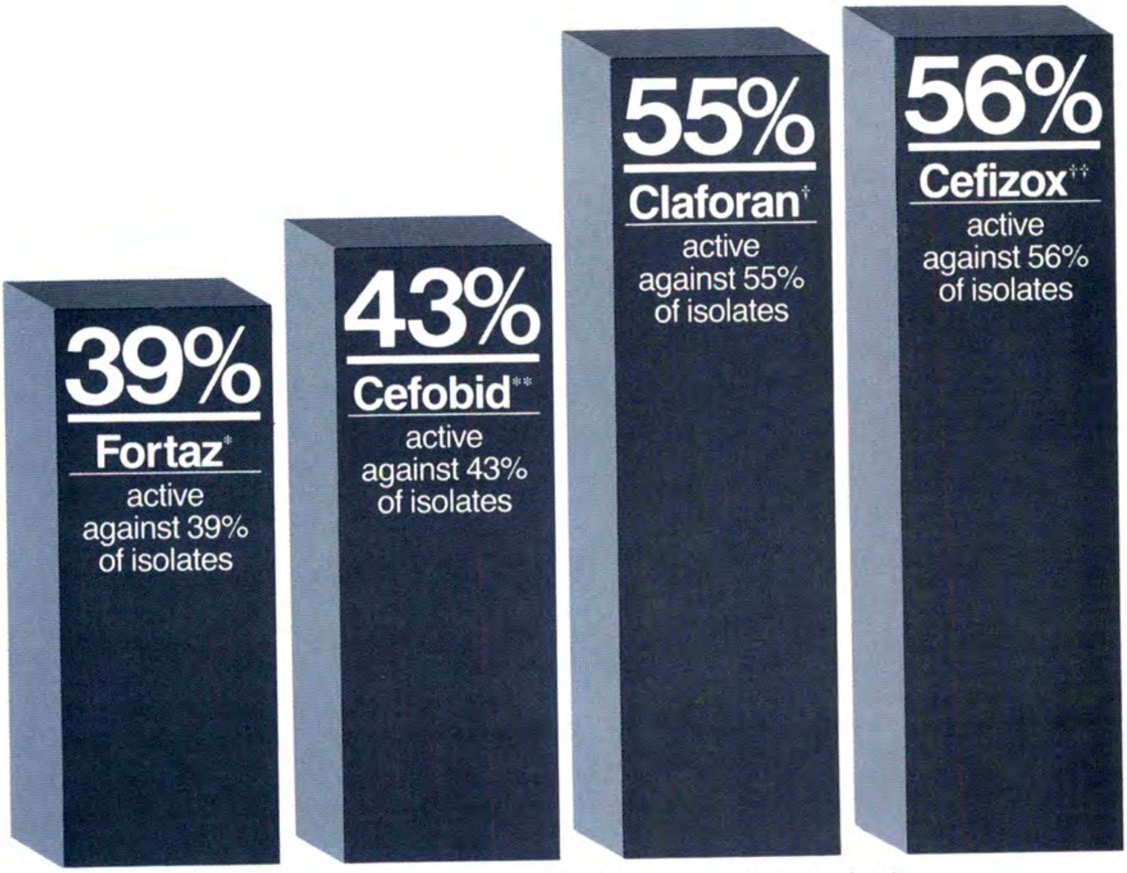

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GENITOURINARY INFECTIONS. Urinary tract infections caused by *E. coli*, *Klebsiella* species, *Proteus mirabilis*, indole-positive *Proteus* (i.e., *P. morganii*, *P. rettgeri*, and *P. vulgaris*), and *Providencia* species. Uncomplicated gonorrhea due to *Neisseria gonorrhoeae* (penicillinase and non-penicillinase producing).

INTRA-ABDOMINAL INFECTIONS, including peritonitis and intra-abdominal abscess, caused by *E. coli*, *Klebsiella* species, *Bacteroides* species including the *B. fragilis* group,§ and *Clostridium* species.

GYNECOLOGICAL INFECTIONS, including endometritis, pelvic cellulitis, and pelvic inflammatory disease, caused by *E. coli*, *N. gonorrhoeae* (penicillinase and non-penicillinase producing), *Bacteroides* species including the *B. fragilis* group,§ *Clostridium* species, *Peptococcus* species, *Peptostreptococcus* species, and group B streptococci.

SEPTICEMIA caused by *Strep. pneumoniae* (formerly *D. pneumoniae*), *Staph. aureus* (penicillinase and non-penicillinase producing), *E. coli*, *Klebsiella* species, and *Bacteroides* species including the *B. fragilis* group.§

BONE AND JOINT INFECTIONS caused by *Staph. aureus* (penicillinase and non-penicillinase producing).

SKIN AND SKIN STRUCTURE INFECTIONS caused by *Staph. aureus* (penicillinase and non-penicillinase producing), *Staph. epidermidis*, streptococci (excluding enterococci, e.g., *Strep. faecalis*), *E. coli*, *P. mirabilis*, *Klebsiella* species, *Bacteroides* species including the *B. fragilis* group,§ *Clostridium* species, *Peptococcus* species, and *Peptostreptococcus* species.

Although appropriate culture and susceptibility studies should be performed, therapy may be started while awaiting these results. Cefoxitin is not active *in vitro* against most strains of *Pseudomonas aeruginosa* and enterococci (e.g., *Strep. faecalis*) and many strains of *Enterobacter cloacae*. Methicillin-resistant staphylococci are almost uniformly resistant to cefoxitin.

Contraindications: Previous hypersensitivity to cefoxitin and the cephalosporin group of antibiotics.

Warnings: BEFORE THERAPY IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE PREVIOUS HYPERSENSITIVITY REACTIONS TO CEFOXITIN, CEPHALOSPORINS, PENICILLINS, OR OTHER DRUGS. GIVE WITH CAUTION TO PENICILLIN-SENSITIVE PATIENTS. ANTIBIOTICS SHOULD BE ADMINISTERED WITH CAUTION TO ANY PATIENT WHO HAS DEMONSTRATED SOME FORM OF ALLERGY, PARTICULARLY TO DRUGS. IF AN ALLERGIC REACTION TO CEFOXITIN OCCURS, DISCONTINUE THE DRUG. SERIOUS HYPERSENSITIVITY REACTIONS MAY REQUIRE EPINEPHRINE AND OTHER EMERGENCY MEASURES.

Pseudomembranous colitis, from mild to life-threatening in severity, has been reported with virtually all antibiotics (including cephalosporins); therefore, it is important to consider its diagnosis when diarrhea develops in association with antibiotic use. Broad-spectrum antibiotics alter normal flora of colon and may permit overgrowth of clostridia; a toxin produced by *Clostridium difficile* is a primary cause of antibiotic-associated colitis. Mild cases may respond to drug discontinuance alone; in more severe cases, management may include sigmoidoscopy, appropriate bacteriological studies, fluid, electrolyte and protein supplementation, and use of a drug such as oral vancomycin; isolation of the patient may be advisable. Other causes of colitis should also be considered.

Precautions: *General*—Total daily dose should be reduced in patients with reduced urinary output due to renal insufficiency because high and prolonged serum antibiotic concentrations can occur from usual doses. Prescribe with caution in patients with a history of gastrointestinal disease, particularly colitis. Prolonged use may result in overgrowth of nonsusceptible organisms; repeated evaluation of the patient's condition is essential. If superinfection occurs, take appropriate measures.

Drug Interactions—Increased nephrotoxicity has been reported following concomitant administration of cephalosporins and aminoglycoside antibiotics.

Drug/Laboratory Test Interactions—High concentrations (>100 mcg/mL) may interfere with measurement of serum and urine creatinine levels by the Jaffé reaction and produce false increases of modest degree in creatinine levels reported; serum samples should not be analyzed for creatinine if withdrawn within 2 hours of cefoxitin administration. High concentrations may interfere with measurement of urinary 17-hydroxy-corticosteroids by the Porter-Silber reaction and produce false increases of modest degree in levels reported. A false-positive reaction for glucose in urine has been observed with CLINITEST‖ reagent tablets.

Carcinogenesis, Mutagenesis, Fertility Impairment—No long-term animal study has been performed on carcinogenic or mutagenic potential. Rat studies at approximately three times maximum recommended human dosage revealed no effects on fertility or mating ability.

Pregnancy Category B—Reproduction studies in rats and mice did not reveal teratogenic or fetal toxic effects, although fetal weights were slightly decreased. In rabbits, cefoxitin was associated with a high incidence of abortion and maternal death, neither considered teratogenic. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers—Excreted in human milk: Exercise caution.

Pediatric Use—Safety and efficacy in infants from birth to three months have not yet been established. In children three months and older, higher doses have been associated with increased incidence of eosinophilia and elevated SGOT.

Adverse Reactions: The most common adverse reactions have been local reactions following intravenous or intramuscular injection. Other adverse reactions have been encountered infrequently. *Local Reactions*—Thrombophlebitis with intravenous administration; pain, induration, and tenderness after intramuscular injections. *Allergic Reactions*—Rash (including exfoliative dermatitis), pruritus, eosinophilia, fever, and other allergic reactions including anaphylaxis. *Cardiovascular*—Hypotension. *Gastrointestinal*—Diarrhea, including documented pseudomembranous colitis during or after treatment, and, rarely, nausea and vomiting. *Blood*—Eosinophilia, leukopenia including granulocytopenia, neutropenia, anemia, including hemolytic anemia, thrombocytopenia, and bone marrow depression. A positive direct Coombs test may develop in some individuals, especially those with azotemia. *Liver Function*—Transient elevations in SGOT, SGPT, serum LDH, and serum alkaline phosphatase. *Renal Function*—Elevations in serum creatinine and/or blood urea nitrogen levels and, rarely, acute renal failure.

Note: In group A beta-hemolytic streptococcal infections, therapy should be maintained for at least 10 days to guard against the risk of rheumatic fever or glomerulonephritis. In staphylococcal and other infections involving a collection of pus, surgical drainage should be carried out where indicated. Intramuscular injections should be well within the body of a relatively large muscle such as the upper outer quadrant of the buttock (i.e., gluteus maximus); aspiration is necessary to avoid inadvertent injection into a blood vessel. The total daily dosage in infants and children should not exceed 12 grams.

How Supplied: Sterile cefoxitin sodium in vials, infusion bottles, and ADD-Vantage®# vials containing 1 gram or 2 grams cefoxitin equivalent and in 10-gram bulk bottles.

§ *B. fragilis, B. distasonis, B. ovatus, B. thetaiotaomicron, B. vulgatus*

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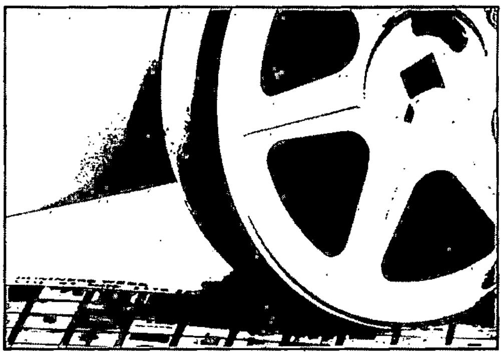

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Defective Glucose Utilization in Patients with Functioning β-Cell Tumors Persists after Tumor Excision

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Glucose utilization was assessed before and after operation in five patients with insulin-secreting tumors using the euglycemic clamp. Two groups of age, sex, and weight-matched controls were studied under conditions of either acute (3 h, $N = 7$) or chronic (48–72 h, $N = 6$) hyperinsulinemia (46 ± 4 μU/mL). The rate of glucose infusion (M = mg/kg/min) required to maintain steady-state euglycemia was taken as index of glucose utilization. M was higher both in postoperative patients and in chronic controls than in preoperative patients (2.1 ± 0.1 and 1.8 ± 0.2 *vs.* 1.0 ± 0.2, $p < 0.01$), yet never achieved levels seen in acute controls (3.3 ± 0.3, $p < 0.01$). Also reported is one subject who had a predominantly proinsulin-producing tumor with little insulin secretion, who also manifested a similar defect in glucose utilization. Excision of this tumor resulted in partial reversal of the peripheral defect in glucose metabolism. In conclusion, chronic endogenous hyperinsulinemia (and hyperproinsulinemia) in humans is associated with a defect in peripheral glucose utilization that is only partially resolved 2 years after tumor removal.

HYPERINSULINEMIA and insulin resistance coexist in several pathologic conditions including obesity,[1] cirrhosis,[2] chronic renal failure,[3] and non–insulin-dependent diabetes mellitus.[4] Conflicting reports exist concerning the developmental sequence of hyperinsulinemia and insulin resistance.[5–9] It has been suggested that the elevated insulin levels represent compensatory pancreatic secretion in response to reduced insulin activity.[18] Most *in vitro* studies, however, indicate a role for insulin in regulating its own biologic response. Cultures of rat adipocytes,[10,11] rat hepatocytes,[12] and rat hepatoma cells[13] and of human skin fibroblast[14] exposed to insulin exhibit reduced insulin activity. The degree of this reduction is directly related both to the duration of insulin exposure and to the concentration of insulin in the media.[11] Possible explanations for this resistance include decreased coupling efficiency between glucose transport and receptor occupancy, receptor "down regulation," and postreceptor defects in insulin responsiveness.[11] The validity of applying conclusions based on these *in vitro* findings to the intact organism has not been established yet.

Chronic peripheral infusions of insulin achieving comparable insulin enrichments to those seen in insulin resistance states have been used to examine the effects of hyperinsulinemia on *in vivo* glucose metabolism. Generally, these infusions resulted in a reduction in target sensitivity to insulin.[15,16] Yet, physiologic portal-to-arterial insulin gradients are not maintained during such infusions, and thus their application to the study of endogenous hyperinsulinemia is still questionable. Patients with functioning β-cell tumors may represent a more accurate model for the study of primary endogenous hyperinsulinemia. Evaluating these patients before and after tumor removal may afford a view into the mechanisms of insulin resistance in humans.

The purpose of this study was to assess the effect of chronic hyperinsulinemia and its normalization on glucose utilization in humans. Glucose utilization was assessed in six patients before and after resection of their β-islet cell tumor using the euglycemic clamp technique originally proposed by DeFronzo et al.[17] The results were compared with those obtained from two groups of well-matched volunteers who served as controls. One group ($N = 7$) had a euglycemic clamp technique used during an acute infusion of human insulin. The second

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TABLE 1. *Characteristics of Insulinoma Patients*

Patient	Age (Years)	Sex	Race	Height (cm)	Weight (kg)	Symptom Duration (mos)	Operation–Study Interval (mos)
1	18	F	W	157	56	4	6
2	22	M	W	170	72	12	24
3	40	M	W	175	75	2	9
4	46	F	W	161	60	24	18
5	76	M	W	170	63	36	0.25
6*	41	M	B	174	65	60	0.50

* Predominantly a proinsulin-secreting tumor.

group (N = 6) had endogenous hyperinsulinemia produced by a 48–72-hour infusion of glucose, near the end of which a 3-hour euglycemic clamp was performed. Plasma insulin levels were similar in all study groups.

Materials and Methods

Subjects

From July 1981 to December 1985, eight subjects with evidence of inappropriate insulin secretion (concurrent plasma insulin level of >25 μU/mL and plasma glucose level of <50 mg/dL during fasting) were admitted to Vanderbilt University Medical Center. Additionally, one patient was admitted with elevated proinsulin levels and low-normal levels of plasma insulin and C-peptide, associated with hypoglycemic attacks. All patients subsequently had operative removal of a single, benign pancreatic β-cell tumor, which was done by tumor enucleation in five patients and distal pancreatectomy in four patients. After operation, no patients required glucose supplementation to maintain euglycemia.

Six of these nine patients had both a preoperative and postoperative euglycemic clamp. The interval from tumor removal to the postoperative study ranged from 7 days to 24 months. The ages of these six patients ranged from 18 to 76 years (Table 1). All recounted symptoms consistent with recurrent hypoglycemia varied from 2 months to 5 years in duration. One patient had been an insulin-dependent diabetic for 25 years and was well controlled with oral hypoglycemic agents. Another patient gave a positive family history of adult onset (non-insulin-dependent) diabetes. Three patients were being treated elsewhere for psychiatric disturbances, and three were taking antiepileptic medications.

Control subjects included 13 normal volunteers without family histories of diabetes mellitus who were matched for age, sex, height, and weight. Seven subjects received a 3-hour infusion of insulin (0.32 ± 0.02 μU/kg/min) and six subjects had a prolonged infusion of glucose for 48–72 hours.

Experimental Protocol

Studies of patients with islet cell tumors were done after an overnight fast. Patients were kept euglycemic with an infusion of glucose *via* an antecubital vein. Plasma glucose levels were monitored every 1–2 hours and maintained near 90 mg/dL by adjusting the infusion rate. The glucose infusion was stopped at 8:00 A.M. on the day of the study, and frequent (15–30-minute) glucose monitoring was continued until plasma glucose levels fell to 50–55 mg/dL. A 3-hour experimental period was begun, during which plasma glucose levels were monitored every 5 minutes and kept between 80 and 90 mg/dL by a variable glucose infusion. Blood for plasma insulin determination was drawn every 15 minutes during the study. In select patients, plasma samples were also obtained at 60-minute intervals for later assay of glucagon, epinephrine, norepinephrine, and cortisol.

The control subjects were also studied after an overnight fast. The placement of catheters (5 cm, 16–18 gauge) into a superficial hand vein (SHVC) and a contralateral forearm vein (FVC) was begun at 7:00 A.M. The hand with the SHVC was inserted into a box heated to 55 C to ensure complete arterialization of blood.[18] The FVC was used for infusion of insulin and glucose. The subjects were allowed to rest for 1 hour before a 3-hour experimental period was begun. Seven subjects received a primed continuous infusion of insulin (Humulin R, Eli Lilly and Co., Indianapolis, IN) at a rate calculated to achieve insulin enrichments in the arterialized hand vein equivalent to those noted in the tumor-bearing patients. Plasma glucose levels were monitored every 5 minutes and were maintained near 80–90 mg/dL by a variable infusion of glucose. This group of volunteers constituted the acute hyperinsulinemic controls. A similar study was performed in patients after tumor removal using exogenous insulin to re-establish preoperative levels of hyperinsulinemia. In the patient with proinsulin-secreting tumor, plasma insulin was raised in the postoperative study to levels noted in preoperative insulinoma patients.

TABLE 2. *Plasma Glucose, Insulin, the Rate of Glucose Infusion to Maintain Euglycemia (M) and Metabolic Clearance Rate (MCR_g) in Patients with Insulinomas and in Normal Control Subjects*

	Glucose (mg/dL)		Insulin (μU/mL)		M (mg/kg/min)	MCR_g (mL/kg/min)
	Basal	Experimental	Basal	Experimental		
Insulinoma patients						
Before operation	34 ± 3	94 ± 4	41 ± 5	47 ± 6	1.0 ± 0.17	1.1 ± 0.20
After operation	88 ± 3	93 ± 5	9 ± 1	39 ± 5	2.1 ± 0.13	2.3 ± 0.20
Control subjects + hyperinsulinemia						
Acute (3 h)	86 ± 2	86 ± 4	8 ± 0.2	44 ± 5	3.3 ± 0.26	3.9 ± 0.20
Chronic (48–72 h)	81 ± 3	83 ± 3	10 ± 0.1	45 ± 4	1.8 ± 0.20	2.3 ± 0.20

Another six control subjects were admitted for 3 days to the Clinical Research Center (CRC) at Vanderbilt. On the day of admission, blood for basal glucose and insulin was drawn and catheters were placed in forearm veins bilaterally to be used for glucose infusion and for blood sampling. Subjects consumed weight-balanced meals on the CRC until fasting was begun at 10 P.M. the night before the study. The glucose infusion was begun on the day of admission at 2.3 g/h and was escalated by 2.3 g/h for 5 hours. Blood samples were obtained every 1–2 hours for the measurement of plasma glucose levels, which were kept near 90 mg/dL by adjusting the glucose infusion rate. The infusions lasted from 48 to 72 hours. A 3-hour experimental period was begun at 8:00 A.M. after 10 hours of fasting. During this period plasma glucose levels were monitored every 5 minutes and kept near basal levels (range: 74–90 mg/dL) for each subject. Blood was obtained at 15-minute intervals for plasma insulin assay and at 30–60-minute intervals for later assays of plasma glucagon, epinephrine, norepinephrine, and cortisol.

In all control subjects and in one patient with β-islet cell tumor, the rate of glucose production was estimated using a primed continuous infusion of 3-[^{3}H]-glucose as previously described.[19,20]

All studies were approved by the Committee for the Protection of Human Subjects. All subjects gave informed written consent before participating in the study.

Analytical Methods

All infusions were performed with a geared motor driven pump (Harvard Infusion/Withdrawal Pump, Model #600–900, Harvard Apparatus, Co., Inc., Dover, MA) using 60-mL syringes. Plasma glucose levels were measured by the glucose oxidase method using a Beckman Glucose Analyzer II (Beckman Instruments, Fullerton, CA). Glucose specific activity in plasma was determined in samples deproteinized with 4.5% barium hydroxide and 4.5% zinc sulfate (1:10, v/v) as previously described.[18] Blood for insulin determination was collected in cold tubes containing EDTA, and plasma samples were stored with Trasylol (500 U/mL) at −70 C for later assay. The insulin assay[21] was performed using a Phadebas radioimmunoassay kit obtained from Pharmacia Laboratories (Pharmacia, Inc., Piscataway, NJ). The inter- and intra-assay coefficients of variation were 6.5% and 7.2%, respectively. The lower limits of the assay were 2–3 μU/mL, and the assay could not differentiate these levels from zero. The antibody used for insulin detection had a 75–90% cross-reactivity with proinsulin. Immunoreactive glucagon levels were assayed as previously described[22] using Unger's 30 K antibody obtained from Southwestern Medical Center (Dallas, TX). Plasma cortisol levels were determined by a Gammacoat RIA kits (Clinical Assays, Travenol-Gennentech Diagnostics, Cambridge, MA) and plasma catecholamines were measured using a radioenzymatic CAT-A-KIT assay kit (Upjohn Diagnostics, Kalamazoo, MI). Proinsulin levels were determined by radioimmunoassay as previously described.[23]

Calculations

In the control subjects and one subject with a β-cell tumor, calculation of the rates of hepatic glucose production (Ra, mg/kg/min) was based on a one compart-

TABLE 3. *Data from One Patient with a Proinsulinoma*

	Basal		Experimental Period	
	Before Operation	After Operation	Before Operation	After Operation
Glucose (mg/dL)	32	90	91	87
Insulin (μU/mL)	1.2	7.2	1.5	41
C-peptide (μU/mL)	<0.05	—	—	—
Proinsulin (μU/mL)	32	—	—	—
M (mg/kg/min)	—	—	1.3	1.9
MCR (mL/kg/min)	—	—	1.4	2.1

* The tumor content of insulin and C-peptide was undetectable.

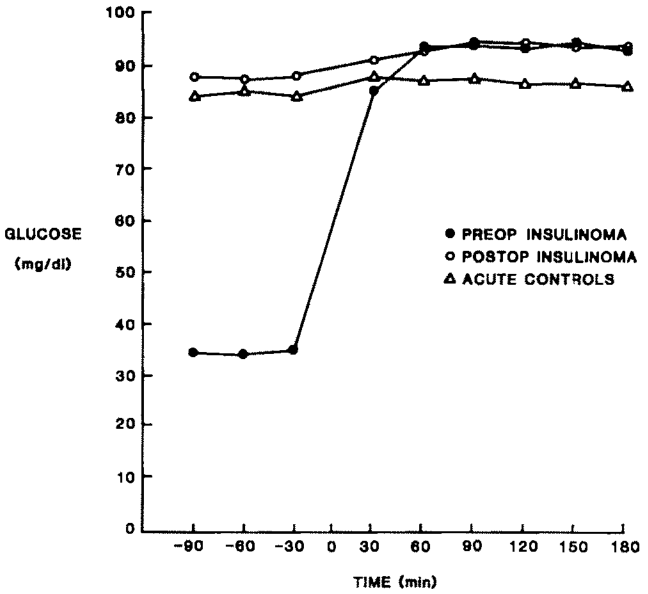

FIG. 1. This diagram represents the temporal changes in plasma glucose concentration during the basal state (−90 to −30 minutes) and during the experimental steady state (60–180 minutes). Basal plasma glucose was significantly depressed before operation (34 ± 3 mg/dL) when compared with any other study group ($p < 0.01$).

ment model as previously described.[19,20] This method has been validated for both insulin and glucose over wide ranges of deviations from steady state.[24,25] The rate of glucose infusion required to maintain euglycemia during the hyperinsulinemic states (endogenous or exogenous) was used as an index of peripheral glucose utilization. This rate was designated as M and expressed as mg/kg/min. The metabolic clearance rate of glucose (MCR_g, mL/kg/min) was calculated as M divided by steady-state plasma glucose (expressed in mg/mL).

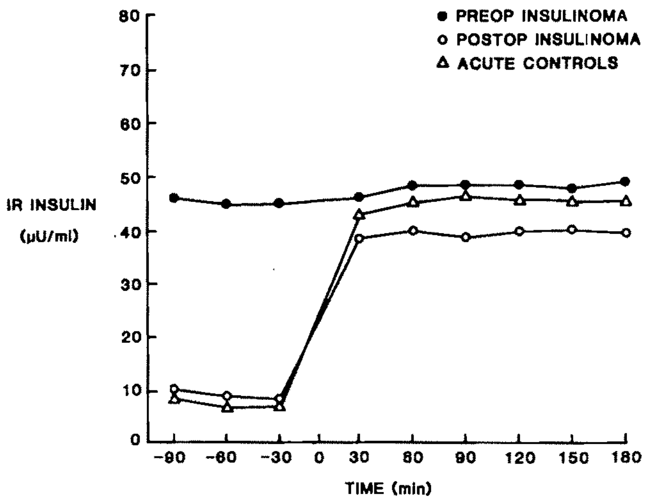

FIG. 2. This diagram represents the plasma immunoreactive insulin levels during the basal state (−90 to −30 minutes) and the experimental steady state (60–180 minutes). No significant difference in steady-state plasma insulin levels existed among the study groups.

Statistical analysis was done using nonpaired t-test, and where applicable, analysis of variance. Data in the Result section, tables, and figures are expressed as mean ± standard error of the mean (SEM), unless otherwise specified.

Results

Of the six patients studied with islet cell tumors, five had proven insulin-producing neoplasms, whereas one patient had a tumor secreting predominantly proinsulin. The results from the study of the patients with insulinomas are presented below and in Table 2. The data from the proinsulinoma patient are presented at the end of this section and in Table 3.

Initial fasting glucose levels were significantly lower in all patients before tumor removal than after tumor resection (34 ± 2.8 *vs.* 84.6 ± 6.2 mg/dL, $p < 0.001$). Glucose levels were maintained at approximately 90 ± 3 mg/dL in all four groups during the hyperinsulinemic euglycemic clamp (Fig. 1).

Basal plasma insulin levels were significantly higher in the insulin tumor-bearing patients than in any other group (Fig. 2). In the preoperative period, basal plasma insulin levels were 41 ± 4 µU/mL and increased slightly in response to the glucose infusion (to 47 ± 6 µU/mL). These levels, however, did not differ from those obtained during the experimental period in the acute or chronic control subjects or in the patients during the postoperative period.

The rate of glucose production was assessed by tracer methodology in one insulinoma patient during the preoperative period and was found to be severely suppressed (basal Ra was 1.6 mg/kg/min, and this value declined to 0.2 mg/kg/min after a 10-hour fast). The induction of hyperinsulinemia resulted in a similar suppression of Ra in the acute and chronic control subjects (Ra dropped from 2.4 ± 0.3 to 0.6 ± 0.2 mg/kg/min in the acute control subjects, and from 2.1 ± 0.4 to 0.4 ± 0.2 mg/kg/min in the chronic control subjects).

The rate of glucose infusion (M, mg/kg/min) required to achieve steady-state euglycemia in the preoperative study was significantly lower than the rate required in the postoperative clamp (1.0 ± 0.17 *vs.* 2.2 ± 0.13, $p < 0.001$). Yet, even after tumor removal, M remained significantly lower than in acute controls (2.2 ± 0.13 *vs.* 3.3 ± 0.26, $p < 0.01$). During chronic hyperinsulinemia induced by glucose infusion, M was found to approach levels noted in postoperative patients (Fig. 3).

In differences in the metabolic clearance rates of glucose (MCR_g), the four study groups mirrored differences noted in M. Thus, even 24 months after tumor resection, the MCR_g remained significantly below levels noted in acute controls (2.6 ± 0.25 *vs.* 3.9 ± 0.37, $p < 0.01$) (Fig. 4).

No consistent relationships existed between preoperative values for insulin and for M, or between duration of symptoms and preoperative M. Furthermore, no association between the absolute or relative changes in M (preoperative to postoperative) and preoperative insulin levels was uncovered.

The levels of the counter-regulatory hormones in the patients with insulin-secreting tumors did not differ from those in the control subjects. Plasma glucagon levels, measured in four patients before operation (145 ± 23 pg/mL), were similar to those measured in the postoperative clamp (106 ± 26 pg/mL) and did not differ from levels seen in control subjects. Similarly, plasma epinephrine (E) and norepinephrine (NE) levels, measured in two patients before operation (121 and 116 pg/mL, respectively) were not different from those seen in the postoperative period (126 and 93 pg/mL, respectively) or in control subjects (acute, E = 105 ± 8 pg/mL, NE = 118 ± 10 pg/mL; chronic, E = 118 ± 13 pg/mL and NE = 121 ± 16 pg/mL). Plasma cortisol levels in two patients with β-islet tumors averaged 4.8 μg/dL before operation, 5.5 μg/dL after operation compared with the acute (6.8 ± 0.9 μg/dL) and chronic (5.9 ± 0.8 μg/dL) controls.

The patient with a proinsulin-producing tumor had depressed fasting glucose levels before operation that stabilized at euglycemic levels after operation without glucose supplementation. Preoperative insulin levels were <2 μU/mL, whereas proinsulin levels were greater than 30-fold above basal. The tumor content of insulin and C-peptide was undetectable. Interestingly, postoperative insulin levels returned almost to normal.

During the preoperative euglycemic clamp, this patient exhibited reduced insulin-like activity (M = 1.3 mg/kg/min; MCR_g = 1.4 mL/kg/min) that improved after tumor removal (M = 1.9 mg/kg/min; MCR_g = 2.1 mL/kg/min). Yet, even after tumor excision, this patient had reduced insulin sensitivity when compared with acute controls (M = 2.1 *vs.* 3.3 mg/kg/min).

Discussion

This study investigated the insulin sensitivity of peripheral glucose utilization in insulinoma patients before and up to 2 years after tumor excision. A state of peripheral insulin resistance was observed in these patients that persisted, although in a milder form, 2 years after correction of the hyperinsulinemia by tumor removal. These findings confirm data recently reported by Rizza et al.[26] and Nankervis et al.[27] We further describe an unusual case of a proinsulinoma in a patient who manifested the same degree of peripheral insulin resistance seen in insulinoma patients. Ten days after removal of the proinsulin-producing tumor, an incomplete improvement was also observed.

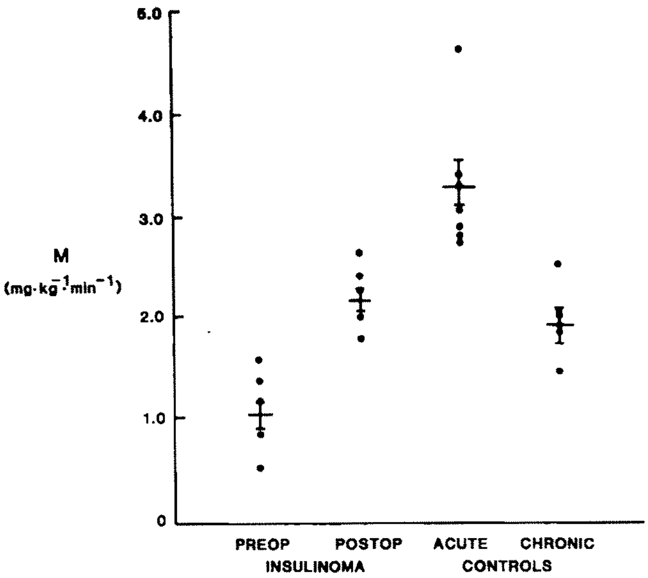

FIG. 3. This scatter diagram represents the values of M, the rate of glucose infused (mg/kg/min) to maintain euglycemia at insulin concentrations of 42 ± 5 μU/mL. Significant differences exist between the preoperative and postoperative M (1.0 ± 0.017 *vs.* 2.1 ± 0.13 mg/kg/min, $p < 0.01$), and between postoperative M or chronic control M and acute control M (2.1 ± 0.13 or 1.8 ± 0.20 *vs.* 3.3 ± 0.26 mg/kg/min, $p < 0.01$).

Insulin resistance was assessed by the hyperinsulinemic euglycemic clamp previously described.[28] This method assumed that the prevailing hyperinsulinemia completely suppressed hepatic glucose production and that the amount of glucose infused to maintain euglycemia reflected peripheral glucose utilization. Plasma insulin levels were identical during the experimental periods in all study groups. In our hyperinsulinemic control subjects and in one insulinoma patient, tracer-

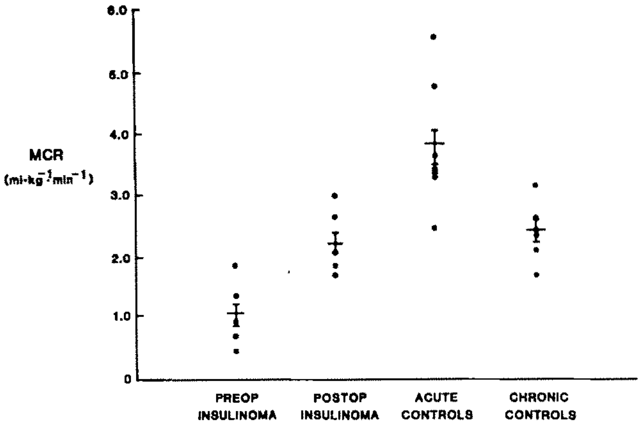

FIG. 4. This scatter diagram depicts the metabolic clearance rate of glucose (MCR_g) calculated as M divided by glucose concentration at steady state. A significant difference existed between the preoperative and postoperative MCR_g (1.1 ± 0.20 *vs.* 2.3 ± 0.20 mL/kg/min, $p < 0.01$) and postoperative and acute control MCR_g (2.3 ± 0.20 *vs.* 3.9 ± 0.20 mL/kg/min, $p < 0.01$).

measured hepatic glucose production was assessed and was found to be 75–80% suppressed by this degree of hyperinsulinemia (42 ± 5 μU/mL). Other studies have shown a comparable degree of suppression of hepatic glucose production occurring in insulinoma patients.[26,27]

Data from the current study also indicate that insulin resistance can be experimentally produced by chronic endogenous hyperinsulinemia resulting from glucose infusion. Hyperinsulinemia was achieved by a 48–72-hour infusion of glucose during which plasma glucose was kept at euglycemic levels. This experimental design, in contrast to previous reports using chronic infusions of insulin,[15,16] should simulate the 2–3-fold portal–arterial insulin gradient seen in normal subjects and in insulinoma patients.[29]

The mechanisms of the resistance to insulin-induced peripheral glucose utilization in insulinoma patients is not well understood. *In vitro* studies have produced conflicting data regarding the effect of high insulin levels on regulation of insulin's activity. Some studies have demonstrated increased insulin activity in tissues preexposed to high insulin levels both *in vivo*[30] and *in vitro.*[31,32] The majority of the reports, however, have shown an insulin-induced decrease in insulin's biologic activity.[11–14,33–36]

In vivo studies in humans[15,16] have shown that peripheral infusions of insulin to create chronic hyperinsulinemia resulted in defective insulin activity even in the presence of normal insulin receptors. Our data using chronic endogenous hyperinsulinemia in the control subjects demonstrated similar defects in insulin activity. Such defects could not be accounted for by changes in counter-regulatory hormones as no rise in circulating glucagon, catecholamines, or cortisol was noted in either control subjects or in select patients with β-cell tumors. Thus, these findings strengthen the possibility that insulin itself or other β-cell secretory products may have directly contributed to the development of insulin resistance.

It is currently believed that chronic hyperinsulinemia is associated with alterations in postreceptor events involved in glucose transport and metabolism in normal volunteers[15,16] and obese subjects[37] as well as in patients with insulinoma,[26,27] chronic renal failure,[37] cirrhosis,[37] and type II diabetes.[37] This conclusion is derived from observations of a reduction in the maximal responsiveness of glucose utilization to insulin that occurred in the presence of normal or mildly reduced insulin receptor number.

The patient with a purely proinsulin-secreting tumor afforded us a unique opportunity to examine the effect of other β-cell secretory products on insulin-like activity *in vivo.* This patient had a severe reduction in peripheral glucose utilization in the presence of low circulating insulin. This finding indicates that the abnormally high levels of proinsulin observed in this patient must have contributed to the development of his insulin resistance. It has been well established that plasma proinsulin levels are elevated in patients with insulinoma and can vary between 30 and 90% of the circulating plasma immunoreactive insulin.[38,39] Thus, elevated proinsulin levels may have contributed also to the insulin resistance seen before operation in insulinoma patients. In addition, proinsulin, once considered to have minimal physiologic activity,[40,41] has recently been shown to have potent insulin-like action in reducing hepatic glucose output in patients with non–insulin-dependent diabetes mellitus.[37] This raises the possibility that the elevated levels of proinsulin in patients with β-islet cell tumors may contribute significantly to the observed reduction in hepatic glucose output and subsequent hypoglycemia.

Insulin resistance in patients with β-islet cell tumors may thus have two components: an insulin (or proinsulin)-induced component that was reversed after tumor removal, and a more permanent defect that persisted long after tumor resection. The persistence of this defect 2 years after tumor removal raises the possibility that this defect in glucose utilization may have existed before tumor development. This defect then would have resulted in subclinical and intermittent hyperinsulinemia that could have worsened the insulin resistance. This continuous and progressive pancreatic stimulation might constitute a predisposing state for the development of an insulin-secreting tumor. An alternative but even more unlikely explanation would be that chronic hyperinsulinemia induces a permanent defect in peripheral glucose utilization. For this to have occurred would have required alterations in the genomic structures responsible for the various proteins that control glucose utilization.

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DISCUSSION

DR. DONALD S. GANN (Providence, Rhode Island): I very much enjoyed this paper, and I would like to thank Dr. McGee and Dr. Abumrad for the opportunity to read the manuscript as well.

The hypothesis that appears to have given rise to this study is an intriguing one. If I understand it correctly, it is that the increase in insulin itself is the cause of decreased insulin sensitivity. Therefore, one would expect that the removal of the insulin source would lead to a restoration of normal sensitivity, which the authors did not find.

The primary question this raises then is: what is the mechanism of this insensitivity that appears to be in part only dependent on insulin? Specifically, I would like to ask, since the authors did not find significant decrease in insulin receptors, what is the mechanism of the post-receptor insensitivity that appears to have been generated? They did find some lowering of receptors, as I understand it, and I would also like to ask what is the contribution of partial down regulation to the observations? However, the most intriguing thing to me about this manuscript seems to be the possibility that, in fact, there is a pre-existing insulin insensitivity. Contrary to the initial hypothesis, this might provide a chronic stimulus to insulin production, which in turn might lead to islet cell hyperplasia and then to the development of autonomous islets and ultimately to the formation of an islet cell tumor. I realize that this is a wild speculation, but I would very much appreciate the author's comments.

DR. WILLIAM R. DRUCKER (Rochester, New York): The study is an investigation of down-regulation. I think most of us interested in this area realize that this is an internal homeostatic mechanism by which the body will adjust to a decrease in various stimuli. In this case the insulin became elevated, by mechanisms yet to be determined, leading to a decrease in the receptors for insulin.

It is fascinating that this change seemed to persist for at least 2 years after excision of the known stimulus, namely, the islet cell tumor. In studying the phenomenon, the authors concocted a model in which they infused glucose over a 48–72-hour period. Thereby they induced an increase in endogenous output of insulin. In itself that will create a desensitization, if you will, or a loss of the receptor mechanism, at least from a functional standpoint.

Therefore, my first question would be: just how long does this iatrogenic decrease in receptor activity last?

To obtain proper control in this study, I believe it is necessary to have some idea of what the surgery itself does in terms of the receptor mechanisms. As you all know, there is much literature, to which Dr. Donald Gann and I also have contributed, about the changes in insulin response following surgery. To what extent does the surgery itself influence the early studies that were performed on these patients?

I am concerned about the influence of the glycogen content in the liver on the results they demonstrated because in the study of the patient with an insulinoma, they did their study after the blood sugar has fallen to 50 mg/dl. At that point they started their study with the glucose clamp. If the blood sugar has fallen to that level, I would expect the glycogen to be virtually depleted in the liver, whereas in their control study the blood sugar was at a normal level when they started their study with the glucose clamp. Do they think this probable difference in hepatic glycogen content may have influenced the results?

My final question is: have they done or are they planning any studies to localize this defect? Have they done any forearm studies to measure the differences in glucose uptake in these patients, and how long the changes last?

I share with Dr. Gann the fascination with the hypothesis put forward by the authors in their article that this may very well be started by an inborn or acquired defect in insulin sensitivity of the insulin receptors in the periphery, leading to a chronic stimulus of the pancreas, and thereby leading to a tumor. My only concern about that hypothesis is that there are a large number of similar clinical situations, some of which are identified by the authors, and I am not aware of the fact that those clinical situations are associated with an unusually high incidence of insulinomas. Perhaps other clinical situations would be worth looking into as one way of testing their hypothesis. Do these other situations in which there is a defect in insulin receptors become associated with insulinomas?

DR. P. BESSEY (Birmingham, Alabama): Drs. McGee, Kulaylat, and Abumrad from Vanderbilt have presented a very interesting study and given us information that again illustrates how illness and surgical treatment may affect glucose and insulin metabolism.

They have used the insulin clamp techniques, originally developed by Rubin Andrews over 25 years ago, to study patients both before and after resection of insulinomas and correction of chronic hyperinsulinemia.

Using the clamp, they have been able to reproduce, both before and after operation, identical conditions of glucose and insulin concentrations. Under those identical conditions, they have observed an apparent difference in the sensitivity to insulin in these same patients. Whole body glucose disposal was approximately doubled after resection of the tumors, indicating that the patients had been insulin-resistant before operation. They also observed that patients were less sensitive to insulin than a group of age, sex, and weight matched controls.

The equating of glucose disposal with glucose uptake should be made with caution. Glucose disposal as measured under the clamp technique may underestimate actual whole body uptake if hepatic glucose production is appreciable. Since the patients presumably had increased activity of the counter-regulatory hormones in response to periods of hyperinsulinemia and hypoglycemia, it may be that the hepatic glucose production was different or differently suppressed in the two periods. Do the authors have any information about that?

Alternatively, as Dr. Drucker suggested, is there any information regarding uptake of glucose across a specific microvascular bed such as the forearm or the leg?

The authors have attributed these observations and changes in the insulin response to alterations in the affinity or occupancy rate of the receptors. Are there other supporting data? For example, have you tried to use higher insulin concentrations so as to saturate the receptors to overcome this apparent receptor defect?

The hypothesis is supported by the experimental group receiving chronic glucose infusions in an induced state of hyperinsulinemia. However, in the patients, may there not be some other mechanisms involved?

Black and associates several years ago presented to this Association information about another group of patients with insulin resistance, namely those recovering from acute injury. They had quantitated insulin resistance, and it appeared to be a postreceptor defect.

We reported information on the effects of hormones on the interactions of glucose and insulin. When normal subjects received a "cocktail" of three stress hormones, hydrocortisone, glucagon, and epinephrine, both glucose uptake across the forearm and whole body glucose disposal were greatly reduced. This appeared to be a cortisol effect. Do the authors have any information about counterregulatory hormone activity in their patients? Were they comparable both before and after operation?

Finally, I have a bit of a concern regarding the difference between the patients after resection of the tumor and the controls. Considering this is a relatively small group, were the patients and controls comparable in terms of body composition and activity immediately before the study?

DR. JOHN F. BURKE (Boston, Massachusetts): Dr. McGee has presented a well carried out and interesting study looking at glucose metabolism in a select group of patients with insulin-producing tumors.

The evidence that there is an insulin receptor, postreceptor complex abnormality, is very persuasive, and I have two questions concerning this concept.

One, since hyperinsulinemia is regularly generated in patients receiving hyperalimentation, do the authors have any idea how long it takes to develop the abnormality they postulate, and are we producing this abnormality in some of our patients?

Second, it is intriguing to believe that perhaps there is more than just an inslulin receptor, postreceptor, problem. Are there metabolic consequences that last? What is the long-term status of the metabolic rate or amino acid metabolism, etc? Are they altered in this state? If so, do they persist?

DR. NAJI N. ABUMRAD (Closing discussion): Obviously this paper has raised many more questions than it has attempted to answer. You all know that we do not see these patients often, and over a 7-year period we took care of only nine patients, and we are currently presenting data on six such subjects.

Many questions have been raised, and I will attempt to answer them one by one:

Dr. Gann asked about the mechanism of insulin insensitivity, and whether it is related to insulin itself or it is a postreceptor defect.

It is currently well established from several *in vitro* and *in vivo* studies that insulin itself can result in both receptor and postreceptor defects, leading to insulin insensitivity. It is possible to speculate in the current study that insulin itself could have caused a permanent defect that resulted in insulin insensitivity. For this to occur, it has to affect the genomic structure of the target cells. *i.e.,* affect the cellular DNA. Currently we are not aware of any data (*in vitro* and *in vivo*) to substantiate such a claim.

The fact that the removal of the pancreatic tumors did not reverse the defect suggests the existence of an already existing genetic defect, which might explain our results. We do not have supporting data for this speculative assumption. We are currently interested in examining whether such a defect actually exists, and as a result we have started collaborative studies to examine this particular issue using specific cDNA probes. We believe that such studies are important as they will shed light on the mechanism of this disease both in a longitudinal and a cross-sectional manner. Furthermore, such studies will enable us to understand whether infants with nesidioblastosis are susceptible to this disease because of the presence of a genetic defect. If true, then we need to examine these patients over a prolonged period to determine whether they will be more susceptible to development of pancreatic adenomas in their pancreatic remnants over time.

Third, could such a defect be due to a change in the receptor number and affinity? As you are all aware, only 10% of cellular receptors are usually occupied, and 90% fit the description of "spare receptors." It is thus difficult to speculate that the defect is due to a decrease in the absolute number of receptors. There is only one known clinical condition where the number of receptors is low, and that is Leprechaunism. Even in such patients, and this will answer Dr. Bessey's question, there is a mild decrease in the total number of insulin receptors, associated with a decrement in hormone-receptor affinity.

Dr. Drucker, your comments are very well taken, and I agree with you that the issue of receptor down regulation is at the heart of the problem. Our studies and those found in the literature indicate that the defect has two components. The first component is due to prolonged exposure to insulin itself, and is responsible for partial resolution of the defect with tumor removal. The second component is most likely due to a postreceptor defect, which is due to down regulation of the receptors. Two groups of investigators have already looked at this problem and both have suggested that the decrement in insulin receptor number cannot account for more than 10% of the defect. Therefore, the majority of the defect is most likely due to down regulation of the receptor, the nature of which is still unknown. This defect could be the result of an alteration in any of the cascade pathways beyond the hormone-receptor interaction that occurs at the cell membrane. Such defects could be in the expression of the second messenger, in adenylate cyclase or in the activation of protein kinase enzymes, or even in alteration in the phosphodiesterase pathways. Currently we have no data to indicate which of these pathways is affected.

Dr. Drucker, your question regarding insulin insensitivity in the normal controls is a very interesting question. We are currently doing studies to establish the length of time it takes normal volunteers to develop insulin insensitivity while they are being exposed to prolonged glucose infusions. We hope to report on such studies in the future.

Dr. Bessey, I appreciate your comments regarding the use of various insulin infusion rates to examine whether this defect in insulin action is due to insulin sensitivity or specificity at the target tissues. Such studies will be performed in the future. With regards to the question that you and Dr. Drucker raised regarding the exact site of insulin resistance, *i.e.,* is it mainly in the liver or the peripheral tissues, we currently do not have any data to incriminate one or the other. As you are aware, the liver is sensitive to insulin's action, and as was shown by Rizza et al., the liver maintains this degree of sensitivity after prolonged exposure to insulin. Therefore, by deduction, I will assume that this defect must be mainly seen in the peripheral tissues, and most likely skeletal muscle. We are currently doing studies using the forearm as a model to examine the role of skeletal muscle in such a defect and the results are still pending. Furthermore, we do not believe that this insensitivity is due to the activation of the counter-regulatory hormones, as glucagon, epinephrine, norepinephrine, and cortisol levels in select patients were not different from those of normal controls.

Dr. Burke, your question regarding insulin insensitivity in patients receiving prolonged TPN is very interesting. We are not aware of any studies addressing this particular issue, and future studies will need to be designed to examine this problem. If I had to guess, I would presume that such a defect does indeed exist in patients receiving prolonged TPN, and I presume that this defect is due to excess carbohydrates and not to excess availability of amino acids.

Finally, Dr. Drucker asked about the differences in glycogen content between the patients and the normal controls. This is an extremely important point to consider. We like you, believe that the normal volunteers are glycogen replete, whereas the patients were most likely glycogen depleted. Therefore, if we assume that most of the glucose infused in the normal volunteers was channelled into repletion of hepatic glycogen stores, there then will be less glucose going to the peripheral tissues, thus augmenting insulin resistance in the periphery. This would result in underestimation of insulin resistance in these individuals, and thus such results would further strengthen our argment already raised, that prolonged endogenous hyperinsulinemia results in insulin resistance.

The Early Fate of Venous Repair after Civilian Vascular Trauma

A Clinical, Hemodynamic, and Venographic Assessment

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Repair of major venous injuries of the extremities has been advocated to improve limb salvage rates and to prevent the early and late sequelae of venous interruption. The contribution of venous repair to the surgical outcome remains controversial, however, in part because the fate of venous reconstruction has previously not been well defined. The current study was done to determine the early patency rate of venous repair; to compare the accuracy of various methods used to assess venous patency, and to analyze the relationship between early venous patency and surgical outcome. During a recent 27-month period, 36 patients with major extremity venous injuries were treated by venous reconstruction; 34 patients (94%) had an associated major arterial injury that also required repair. Venous repair was performed in the upper extremity (22%) as well as the lower extremity (78%) using various reconstructive methods, including lateral repair (17%), end-to-end anastomosis (11%), autogenous vein patching (25%), interposition autogenous vein grafting (42%), and panelled autogenous vein grafting (6%). After operation, venous repair patency was evaluated by clinical examination, impedence plethysmography, and Doppler ultrasonography, and contrast venography. There were no perioperative deaths in these 36 patients. The limb salvage rate was 100% and all 34 major arterial repairs were patent at the time of hospital discharge. Venography performed on the seventh postoperative day demonstrated that 14 venous repairs had thrombosed (39%) and that 22 had remained patent (61%). Local venous repair had a significantly lower thrombosis rate (21%) than those requiring interposition vein grafting (59%) ($p < 0.03$). Compared with venography, the clinical evaluation was 67% accurate in the assessment of venous repair patency, and the noninvasive examination was 53% accurate. In conclusion, a substantial percentage of venous repairs will thrombose in the postoperative period, especially if interposition vein grafting is used. However, in this series limb salvage was not adversely influenced by an unexpectedly high rate of venous repair thrombosis. In addition, clinical evaluation and noninvasive testing did not provide an accurate assessment of venous patency after venous repair.

THE OPTIMAL MANAGEMENT of major venous injuries continues to be a controversial topic. Although successful venous repair was reported as early as the latter part of the 19th century, ligation of major venous trauma was the accepted method of treatment during World Wars I and II.[1,2] Hughes reported on repair of selected cases of venous injury during the Korean War,[3] but it was not until the Vietnam conflict that routine repair of venous injuries was advocated by Rich and Hughes.[4] Most reports from the civilian sector during the post-Vietnam era continued to encourage an aggressive approach towards major venous trauma,[5-9] but several recent publications have questioned the necessity of routine venous repair, citing good results in selected patients with venous injuries managed by primary ligation.[10-12]

The contribution of venous repair to the surgical outcome remains an unresolved issue, in part because the fate of venous reconstruction has previously not been well defined. This study was done to determine the early patency rate of venous repair, to compare the accuracy of various methods used to evaluate venous patency, and to assess the relationship between early venous patency and surgical outcome.

Patients and Methods

From January 1985 to March 1987, 36 patients with major venous injuries to the upper or lower extremity

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were treated by venous reconstruction on the Vascular Surgery services at Cook County Hospital and the University of Illinois Hospital in Chicago. There were two females (5%) and 34 males (95%), and the age ranged from 16 to 63 years with a mean age of 27.5 years. Thirty-four patients were evaluated immediately after injury. Two patients, both with traumatic arteriovenous fistulae, were seen at 2 months and 18 months, respectively, after injury.

The mechanism of injury included gunshot wounds in 24 patients, lacerations or stab wounds in six patients, shotgun wounds in four patients, and blunt injuries associated with motor vehicle accidents in two patients (Table 1). The diagnosis of major venous injury was made in the operating room in all cases except in those with preoperative clinical or arteriographic evidence for an arteriovenous fistula. Preoperative venography was not used in any instance. Venous injuries were seen in the upper extremity (22%) as well as the lower extremity (78%) and are listed by location in Table 2. Antecubital venous injuries were included in three patients who sustained complete neurovascular disruption at the elbow joint after severe laceration. Associated major arterial injuries were seen in 34 patients (94%) and are listed in Table 3. Associated fracture requiring concomitant stabilization was seen in seven patients (19%), and associated nerve damage of varying degree was seen in 12 patients (33%).

The methods used to reconstruct the injured veins and arteries is summarized in Table 4. Systemic heparin was used routinely during vascular reconstruction except when there was concern about excessive bleeding within the wounds or into other injured body cavities. Distal venous thrombus, if present, was extracted using catheter thrombectomy, and venous repairs were done using interrupted or running monofilament suture. Adjunctive fasciotomy was performed when clinically indicated in 11 patients, all with lower extremity injuries.

After operation, all extremities were elevated until edema, if present, was resolving. On the seventh postoperative day, all patients had Doppler ultrasound and impedence plethysmography evaluation of the extremity to assess venous patency; this was followed by contrast venography. Systemic anticoagulation was given to patients demonstrating deep venous thrombosis on venography. Symptomatic pulmonary embolus was not clinically suspected nor diagnosed in any case. Prospective data on these 36 patients was then analyzed after 27 months using Cochran-Mantel-Haenszel statistic.

TABLE 1. *Mechanism of Injury*

	N	%
Gunshot wound	24	67
Laceration/stab wound	6	17
Shotgun wound	4	11
Blunt injury	2	5
Total	36	100

TABLE 2. *Venous Injuries by Location*

	N	%
Subclavian	3	8
Axillary	2	5
Antecubital	3	8
Common femoral	5	14
Superficial femoral	15	42
Popliteal	8	23
Total	36	100

Results

There were no perioperative deaths in these 36 patients. The limb salvage rate was 100%, and all 34 major arterial repairs were patent by clinical evaluation and noninvasive testing at the time of hospital discharge. Venography performed on the seventh postoperative day demonstrated that 14 venous repairs had thrombosed (39%), and that 22 had remained patent (61%). Venous repair patency was analyzed by location of re-

TABLE 3. *Associated Major Arterial Injuries*

	N	%
Innominate	2	6
Subclavian	1	3
Axillary	1	3
Brachial	3	9
Common Femoral	2	6
Superficial femoral	17	50
Popliteal	8	23
Total	34	100

TABLE 4. *Methods of Vascular Repair*

	No.	%
Venous repair (N = 36)		
Lateral repair	6	17
End-to-end repair	4	11
Vein patch	9	25
Vein graft	15	42
Panelled vein graft	2	5
Total	36	100
Arterial repair (N = 34)		
End-to-end	1	3
Vein patch	5	15
Vein graft	26	77
Prosthetic	2	5
Total	34	100

TABLE 5. *Venous Patency by Location of Repair*

	Patent	Occluded	Total	% Occluded
Subclavian	3	0	3	0
Axillary	2	0	2	0
Antecubital	1	2	3	67
Common femoral	4	1	5	20
Superficial femoral	9	6	15	40
Popliteal	3	5	8	63
Total	22	14	36	

TABLE 6. *Venous Patency by Type of Repair*

	Patent	Occluded	Total	% Occluded
Lateral repair	5	1	6	17
End-to-end repair	4	0	4	0
Vein patch	6	3	9	33
Vein graft	6	9	15	60
Panelled vein graft	1	1	2	50
Total	22	14	36	

pair (Table 5) and type of repair (Table 6). Local venous repair (lateral repair, end-to-end anastomosis, and vein patch repair) had a significantly lower thrombosis rate (21%) than those requiring interposition vein grafting (59%) ($p < 0.03$) (Table 7). There was no significant difference in patency rates between upper *versus* lower extremity venous repair, or between large vessel (subclavian, common femoral, and superficial femoral vein) venous repair *versus* small vessel (axillary, antecubital, and popliteal) venous repair. Four patients were discharged from the hospital with mild lower extremity edema. Review of these four patients venograms revealed venous repair patency in one patient and venous repair thrombosis in three patients. Follow-up evaluation at 3 months demonstrated resolution of edema in two patients and improvement but persistence of edema requiring elastic compression stockings in two patients. Overall, two of 14 patients with venous repair thrombosis had persistent mild lower extremity edema at 3-month follow-up compared with 0 of 22 patients whose repairs were demonstrated to be patent ($p > 0.05$).

TABLE 7. *Patency of Local Versus Extended Repair**

	Patent	Occluded	Total	% Occluded
Local repair	15	4	19	21
Extended repair	7	10	17	59
Total	22	14	36	

* $P < 0.03$.

TABLE 8. *Accuracy of Clinical and Noninvasive Evaluation in Determining Patency of Vein Repair*

	N
Clinical evaluation*	
True (+)	6
True (−)	18
False (+)	4
False (−)	8
Noninvasive testing†	
True (+)	6
True (−)	13
False (+)	9
False (−)	8

* Accuracy = 0.666, positive predictive value = 0.60, negative predictive value = 0.69.

† Accuracy = 0.527, positive predictive value = 0.4, negative predictive value = 0.62.

Compared with contrast venography, the clinical examination was 67% accurate in the assessment of venous repair patency, with a negative predictive value of 0.692 and a positive predictive value of 0.6. Compared with venography, the noninvasive venous evaluation was 53% accurate in the assessment of venous repair patency, with a negative predictive value of 0.62 and a positive predictive value of 0.4 (Table 8).

Discussion

The surgeon's prime objective in the management of major venous trauma is to prevent exsanguination. Once hemorrhage has been controlled, an organized decision must be reached about the best management of the venous injury: whether to ligate this injury or to perform venous reconstruction. The factors that influence this decision include the underlying condition of the patient, the severity of associated injuries, and the complexity of the proposed venous repair.

Nearly everyone would agree that venous repair should be done when it can be performed quickly and safely in an otherwise stable patient. The controversy that has emerged during the past decade centers around the extent to which venous reconstruction should be attempted in less than ideal circumstances.

The arguments for an aggressive approach to even extensive venous injuries have included improvement in limb salvage and a reduction in the acute and chronic sequelae of venous interruption.[4,5,8,13,14] To attribute improvement in surgical outcome to the performance of vein repair *versus* ligation, however, presupposes that the vein repairs have remained patent. Careful review of the literature, however, demontrates that a critical evaluation of the postoperative fate of venous reconstruction has been made in only a handful of patients.[7,9,14,15] To determine whether venous repair has a beneficial effect on surgical outcome, therefore, an analysis of the fate of venous repair is essential.

Contrast venography must be considered the gold standard in evaluating the integrity of the superficial and deep venous circulation. Several previous studies have used postoperative venography to assess the patency of venous reconstruction after venous trauma. Sullivan and co-workers, reporting from the 12th evacuation hospital in Vietnam, determined that seven of 11 popliteal vein repairs were patent by venography performed between 1 and 4 days after operation.[14] Hobson et al. confirmed patency of 13 of 19 femoral venous repairs with postoperative venography.[9] Snyder et al. demonstrated that three of ten popliteal venous reconstructions were patent venographically,[15] and Agarwal and co-workers found that zero of four iliac and femoral vein repairs were patent using postoperative venography.[7] Our data support the contention that a substantial percentage of venous reconstructions will thrombose in the postoperative period (39%). When vein grafting techniques were used, the number of thrombosed repairs in our series was nearly 60%. It is unlikely that this high rate of venous repair failure is a reflection of compromised surgical technique; arterial repair patency and limb salvage rates of 100% indicate that reasonable surgical care was provided to these patients. It is more likely that these results accurately reflect the early natural history of venous reconstruction performed for trauma.

Previous investigators have reported on the inaccuracy of the physical examination in determining the status of venous repair.[10,14] This study supports the finding that clinical markers for the early fate of venous reconstruction are inaccurate, with a high rate of false-positive and false-negative impressions. Surprisingly, impedence plethysomography and Doppler ultrasonography, when compared with contrast venography, were even less accurate in determining whether the venous repair was patent or thrombosed. These results strongly support the use of routine postoperative venography in determining the status of vein repair.

A central and unresolved issue in the repair *versus* ligation controversy continues to be disagreement about the relationship between the method of venous injury management and the surgical outcome. Rich and Hughes,[4] Sullivan et al.,[14] and Phifer et al.[5] have implicated venous ligation as a contributing factor to lower extremity amputation in patients with femoral and popliteal venous trauma. In contrast, Mullins et al.[10] and Timberlake et al.[12] reported no increased risk for extremity amputation in patients with venous injuries managed by ligation. Our data support the concept that maintenance of outflow from the extremity through the main venous conduit is not essential for limb salvage. This was an unexpected finding in our series, especially at the popliteal level where five of eight popliteal vein repairs thrombosed without any case of limb loss.

The effectiveness of venous reconstruction *versus* ligation in the prevention of postoperative edema and later postphlebitic syndrome is also a contested issue. Rich and co-workers reported a 51% incidence of significant edema in patients with popliteal venous injuries managed by ligation compared with a 13% incidence if venous repair was attempted.[13,16] Mullins et al. demonstrated a 23% incidence of mild edema in patients with lower extremity venous injuries managed by ligation.[10] Timberlake and others reported that although transient edema developed in up to 32% of patients managed by venous ligation, no patient had a permanent problem with extremity swelling on long-term follow-up.[12] In the current study, no patient (0 of 22) with venous repair patency had edema at 3 month follow-up, compared with 14% (2 of 14 patients) when venous repair thrombosis had occurred; the difference between these figures was not statistically significant. Long-term follow-up to determine the incidence of delayed venous insufficiency in these groups is essential, but unfortunately is not available currently.

It has been suggested previously that even short-term patency (1–3 days) of venous repair may allow for increased venous outflow from the extremity before the development of collateral venous channels that are stimulated at the time the primary repair undergoes thrombosis.[17] This would be difficult to prove without knowing the exact time at which repair thrombosis occurs. More likely, patients with early occlusion of vein repairs have the same hemodynamic alterations and clinical outcome as those undergoing primary ligation of the injury. Experimental and clinical evidence have suggested that autogenous grafts placed in the venous system which thrombose might recanalize at a later date, possibly preventing delayed venous insufficiency that would occur if ligation had been carried out.[18,19] If segmental occlusion of the vein grafts occurs with preservation of the proximal and distal native venous valves, then graft recanalization may play a role in the maintenance of venous competence. On the other hand, more extensive thrombosis involving the native vein that results in significant valvular damage during recanalization will more likely result in the development of a postphlebitic limb.

Under what circumstances, then, should venous repair be attempted? This study has demonstrated that local repair, including lateral venorraphy, end-to-end repair, and limited vein patching have an acceptable early patency rate of nearly 80%. Local repairs can be performed relatively quickly, and in the case of lateral repair, actually may be an integral step in controlling hemorrhage. When the venous injury is limited enough to allow for local repair, it should be performed routinely, except in those patients too unstable to tolerate the modest increase in operating time.

The decision regarding extended venous repair is a more difficult one; when, if ever, should it be performed? Extended repairs are more complex and time-consuming procedures, and for patients with venous injuries so extensive as to preclude local repair, the decision to perform primary venous ligation can be made more liberally. Our data demonstrate questionable merit to venous repair using vein grafting techniques: the early thrombosis rate was high (59%), and the limb salvage was identical whether these extended repairs were shown to be patent or occluded. Although this study did not demonstrate a statistically significant difference in the incidence of dependent edema at 3 months in patients with patent venous repairs compared with patients with thrombosed repairs, 5- and even 10-year follow-up evaluation will be required to determine if there is a measurable difference in the incidence of delayed venous insufficiency between the two groups. Clearly, no perioperative morbidity can be attributed to our efforts at extended vein repair in these 17 patients, but whether any good was done remains an arguable point.

To summarize, this prospective study has demonstrated that the early thrombosis rate of venous repair is substantial (39%). Local venous repairs had a significantly lower thrombosis rate (21%) than those requiring extended repairs (59%). Limb salvage in this series was not affected by whether venous repair was patent or thrombosed. In addition, the clinical and noninvasive evaluation of venous repair patency were shown to be inaccurate, prompting a recommendation for the use of routine postoperative venography.

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DISCUSSION

DR. NORMAN M. RICH (Bethesda, Maryland): This is a challenging subject that has dominated many of our clinical and research activities at Walter Reed and in military surgery in general for more than 20 years. I would like to thank the authors for sending me their manuscript to review. I have been aware of their work for some time and have encouraged them on a number of occasions.

I would like to comment on several aspects of their report recognizing there are many areas that could be selected. First, and extremely significant, I would like to emphasize the concerns that many surgeons expressed as recently as 15 years ago that the vast majority of patients with attempted venous repair would develop thrombophlebitis and/or pulmonary emboli.

We have been able to refute these concerns through a combined effort, and the authors as well as authors in other civilian series have corroborated these findings on recent years.

The authors have re-emphasized what we all know, that some extremity veins can be ligated without sequelae. Remaining questions identify the challenge: are there patients, and how many patients, where there can be a difference? We found that in lower extremity venous ligation that some amputations were required because of acute venous hypertension.

Another aspect of our long-term follow-up that prompted our interest in this subject was the increasing number of individuals with ligated lower extremity veins, and I emphasize lower extremity veins, who returned years later with all the chronic sequelae of the postphlebitic syndrome. I would offer and challenge those who have had recent reports with 3-month follow-ups and 6-month follow-ups that these follow-ups are absolutely inadequate to know the long-term manifestations of interrupting lower extremity veins.

As Harvey pointed out in the 17th century, and as those who replant extremities know, venous return is of paramount importance.

Finally, the authors are to be congratulated on their success in venous repair. I take the optimistic approach. They document a 61% patency rate. I believe their success rate is excellent, and I would like to ask the authors how many different surgeons were involved in these repairs because as Dale and DeWeese showed 35 years ago, and we corroborated in our laboratory, with a certain amount of experience (as we have been hearing all day, experience is important) dramatic increase in patency rate by an individual surgeon can be achieved.

These experiences are important for us. There are many other aspects to consider from the ideal venous conduit, to the inconsistent venous anatomy, to adjuvant therapy, to recannulization of veins, to pathophysiology as reported and championed by Hobson and Wright, and many other complex considerations. I believe the fact that there are seven people to discuss this presentation emphasizes the interest in this subject at this time. I anticipate that this will remain a significant challenge for us in the future.

Dr. Charles E. Lucas (Detroit, Michigan): Twenty years ago, we were taught that civilian venous injuries were best ligated. Primary venous repair, purportedly, thrombosed thus, increasing the risk for pulmonary embolism. During the 1970s, primary venous repair was used more frequently by most centers, including our own, when the repair could be done easily and the patient was hemodynamically stable. Richard Mullins, in 1980, reported 3 years of our data in a paper that highlighted the natural history and recommended therapy after venous ligation. Although most of our patients treated during those 3 years had primarily venous repair, we are often misquoted as recommending routine venous ligation. Needless to say, we are quite pleased by this since it is far better to be quoted incorrectly than to not be quoted at all. That is from Confucious several centuries B.C.

The 1980s controversy centers around how aggressive one should be with primary venous repair when vein graft interposition is needed and the patient has associated injury. Both sides of the controversy regale the listener with either clinical or noninvasive studies supporting each respective conclusion. The ratio of published papers to patients with postoperative venograms is about 2/1. Dr. Meyer and co-workers have added to the controversy something different, namely, hard data. Based on this hard data, I concur with their following conclusions: (1) simple primary venous repair is almost always indicated; (2) complicated venous repair is indicated only when the patient setting is not unduly compromised; (3) venous thrombosis has minimal effect on the patency of associated arterial repair; (4) the need for fasciotomy is influenced more by distal ischemia from associated arterial injury or associated soft tissue injury as evidenced by the fact that they had the same number of fasciotomies after primary venous repair as we had after primary venous ligation; and (5) long-term venograms 5–10 years later are still needed.

I disagree with one conclusion, namely, that anticoagulation is needed when deep venous thrombosis is confirmed by venography. Dr. Meyer, assuming that the rest of us have the same incidence of unsuspected venous thrombosis after primary venous repair, then dozens of such patients have been treated without anticoagulation. I have not seen such a patient develop a pulmonary embolus. Have you?

Dr. John J. Bergan (Chicago, Illinois): This paper is important because it describes the fate of modern day venous repair in a major accident hospital and does so objectively.

The three conclusions drawn from the paper are well supported, and I want to repeat them for you.

Pulmonary embolus after failed venous repair is not a threat in patients who sustain trauma and have their repair done. Second, achievement of patency in venous repair is disappointing. It is a surprising fact that interposition grafting is associated more with failure than local repair. That is contrary to some research work on this subject. Finally, extremity edema does not occur if the repair stays patient. The conclusion I take from that is that if venous repair can be done, venous repair should be done. Therefore, the questions are: why do the interposition grafts fail? Dr. Meyer, is that a question of disparity of size? Are small saphenous vein grafts being put into major larger veins? If size disparity is not the problem, is it redundancy?

If we are to increase the patency of our repairs, would paneled grafts be better? They were not in your two experiences. Would a spiral graft be better in a major vein?

Dr. R. Rhodes (Cleveland, Ohio): I want to congratulate the authors on an excellent clinical series and particularly Dr. Meyer for a well-presented paper. I do share some of Dr. Rich's concerns, however, that occlusion of the vein graft at 1 week is not necessarily the equivalent of adopting a nonrepair philosophy. I certainly would second his comments regarding the late sequelae of venous occlusion.

I would like to ask a question regarding the relatively high false-negative rate that was seen with the noninvasive venous studies. This suggests that possibly the thrombosis of the venous repair was not a major restrictive factor in venous outflow from the limb. If it is not such a restrictive factor, then perhaps the excellent results with the arterial repair can be explained on the basis of the excellent collateral circulation.

If the authors are proposing an alternative approach to repair, would they suggest a selective approach and would this selective approach be based on preoperative noninvasive venous testing to identify those patients in whom the venous injury is providing venous occlusion and, thus, subsequent restriction of arterial inflow?

Dr. Robert W. Hobson, II (Boston, Massachusetts): I wish to compliment the authors on bringing to our attention the potential value of universal venous reconstruction for major venous injuries of the upper and lower extremity, and yet the data may not be definitive when venous patency is related to limb salvage or amputation rates. My initial comments relate to combining upper and lower extremity venous injuries. Amputations are reported rarely in cases of upper extremity venous injury treated by ligation, which therefore tends to skew your data toward limb survival regardless of venous patency. I recommend an emphasis on lower extremity venous injuries, particularly popliteal and common femoral injuries, which are of greatest clinical significance.

I do not regard universal venous repair as necessary. Based on our investigative and clinical studies, the most important subset of patients would appear to be those with major venous injuries and evidence of peripheral venous hypertension. I ask Dr. Meyers whether peripheral venous pressure measurements were performed or clinical notes recorded on presence or absence of venous distension on his patients in an effort to identify the subset of patients who might benefit most from venous repair?

Second, since the noninvasive vascular laboratory was inaccurate in the analysis of postoperative patency, I question of timing of venography on the seventh postoperative day. Adverse hemodynamics associated with venous occlusion that might influence limb survival occur within the first 48–72 hours after ligation or failed venous repair. Do you have any venographic data on immediate postoperative venous patency? Patency of a major venous repair at that time may ensure survival of the extremity, even though the repair may have occluded by the seventh postoperative day.

Dr. Watts R. Webb (New Orleans, Louisiana): Our experience at Tulane and at Charity Hospital Service, monitored primarily by Dr. Morris Kerstein and published in the *Journal of Vascular Surgery*, recently looked at 156 vascular injuries in 223 patients since 1979. Of this group, there were 83 patients who had venous injuries. Twenty-three of these patients had isolated venous injuries and the rest were associated with arterial injuries. Seventeen patients had venous injuries of the major veins of the arm, not of the trunk, but just of the arm. All were ligated and subsequently there have been no sequelae evidenced at all; therefore, we do not believe that these need to be repaired.

In the leg, about half the injuries were repaired and about half were simply ligated except for the popliteal, which we always repaired, usually with vein grafts. We ligated the veins if the condition of the patient, because of other injuries or because of shock, indicated that it would be better not to spend the time in a detailed repair.

There has been no limb loss in this group. The arteries have stayed open. One thing we have done that perhaps has been slightly more aggressive is utilization of early fasciotomy, in anyone who has the slightest sign or symptom of a compartment syndrome. About 80% of those with combined arterial and venous injuries, and all of those with popliteal combined injuries, and about 70% of those with only venous injuries of the leg have had fasciotomies.

The long-term follow-up after nearly 8 years has demonstrated that about 25 or 30% of those with ligation of the leg veins are going to have some minor disability. The major disabilities occur only in those with nerve injury. In those who have had veins ligated, about one fourth have some minor swelling, which has been controlled easily with elastic stockings.

We would like to say that this experience does not negate or deny the beautiful documentation and experience of military injuries of Dr. Hughes and Dr. Rich, but we do believe that there is a tremendous difference in the populations that we see. In military casualties the injuries have usually disrupted more than one vein, multiple veins, including all the collaterals, and in these patients there is no doubt that it is extremely important that every attempt be made to repair the vein or veins.

We similarly agree that at this time if it is at all feasible and the condition of the patient allows, then one should repair lower extremity veins; but if this is not feasible because of the condition of the patient, then fortunately the long-term consequences probably are not going to be disastrous.

DR. JAMES W. MAY JR. (Boston, Massachusetts): I enjoyed the paper very much.

Virchow has taught us that stasis is related to freshly repaired anastomosis thrombosis. I would like to ask Dr. Meyer if there was a correlation in those repairs that thrombosed with patency of other collateral veins within that extremity. In other words, did the repairs stay patent that needed to stay patent and those thrombose that did not need to stay patent?

DR. JOSEPH MEYER (Closing discussion): I want to thank everyone for their thoughtful comments. I will do my best to answer your questions.

We believe this study has helped to define the early fate of venous repair and the relationship between venous patency and limb salvage. The unexpectedly high rate of venous repair thrombosis has demonstrated to our satisfaction that maintenance of venous patency in the acute setting after a major venous injury is not necessarily required to achieve limb salvage.

Another central issue, which several of our discussants have identified, centers around the long-term sequelae of venous interruption. The 3-month follow-up obtained in our group of 36 patients is clearly insufficient to offer much useful clinical information. Large civilian series reported from Detroit and New Orleans have demonstrated a remarkably low rate of chronic venous insufficiency in patients whose major venous repairs were managed by primary ligation. In contrast, data reported from Viet Nam suggest that late morbidity (at 5- and 10-year follow-up) related to postphlebitic syndrome was substantially higher in patients undergoing venous ligation compared with those with attempted venous repair. These divergent conclusions indicate that the issue remains largely unresolved and will likely remain so until long-term follow-up data, which include venography and hemodynamic testing are available for analysis.

Dr. Rich, most of these patients were treated at Cook County Hospital and had their procedures performed under my supervision. All 36 of our patients were staffed by fellowship-trained vascular surgeons who personally scrubbed in and supervised on each operation to ensure the best possible result.

Dr. Lucas, the natural history of venous repair thrombosis has not been well documented, but we have no reason to believe it should be much different from that of garden variety deep vein thrombosis. Our concern has been that these patients may be at an increased risk for pulmonary embolus (although we have no scientific basis for this) and thus they have been given 3 months of oral anticoagulation.

Dr. Bergan, we were initially surprised at our rather poor results with venous reconstruction, especially when extended vein repairs were performed. As time went on, however, we realized that a substantial number of our repairs were failing, without affecting our overall surgical results. These were particularly unexpected findings at the popliteal level, where five of eight of our venous repairs thrombosed without a case of limb loss. This did not appear to be a function of size discrepancy between the native vein and vein graft, as the results were worse at the popliteal level (where there is less size discrepancy) than at the superficial femoral level.

Why are these vein grafts occluding at higher rates than the local venous repairs? The answer probably lies at the cellular level. The amount of interface between the blood and that portion of the repair that is not native vein may alter thomboxane production and platelet aggregation to stimulate the clotting of blood. This is a question that we will have to refer to the laboratory.

Regarding the technical performance of these procedures, we did use the same meticulous care in repairing the veins as we did the arteries. My impression from reviewing our intraoperative photographs was that they were satisfactory from a technical standpoint. Intraoperative completion angiography was used routinely in these cases, but completion venography was not; this may have helped to detect any intraluminal defects and might have improved our overall results.

Dr. Rhodes, if either the IPG or Doppler ultrasound was incorrect compared with venography, that patient was considered to have an incorrect noninvasive examination. The large number of false-negative noninvasive examinations probably is a reflection of the excellent potential collateral venous circulation in these young patients. We have not used the noninvasive evaluation selectively to determine which vein injury should be repaired and which should be ligated, but I believe it is an interesting idea.

Dr. Hobson, your point about our results being skewed toward the favorable side because of the number of upper extremity venous injuries we included is a good one. Upper extremity venous ligation has been shown to be well tolerated by a number of investigators. It is probably related to the superior venous collateral bed in the upper extremity compared with the lower, and also with the lower hydrostatic pressure in the arm than in the leg in the upright patient. Nonetheless, 80% of our venous injuries were in the lower extremity, and the surgical results were uniformly satisfactory regardless of the anatomic location of the injury.

Peripheral venous pressure measurements were not performed, but venous pressure was clinically elevated in many patients after restoration of arterial flow to the extremity. It is dramatic to remove your distal venous clamp and see a jet of venous blood squirt across the operating table.

Postoperative venography was not performed on the first day after surgery primarily for practical reasons. Many of these patients remained intubated, or had chest tubes or fresh thoracotomies or craniotomies. We believed that a trip down to the x-ray suite under these conditions would be hazardous, and we arbitrarily chose the seventh postoperative day because most patients were stable by then. This approach, unfortunately, did not tell us when our repairs were thrombosing, only what their status was at day seven.

I would like to conclude by offering our recommendations on the management of major venous injuries. The surgeon's primary objective in the management of venous trauma is to prevent exsanguination. Once this has been accomplished, a decision must be reached about the most appropriate management of the venous injury, to ligate or repair. The factors that will influence this decision include the underlying condition of the patient, the severity of associated injuries, and the complexity of the proposed venous repair. Our data indicate that local venous repair has an acceptable early patency rate of 80%, is generally a rapid procedure, and in the case of lateral venorraphy actually may play an integral rôle in controlling hemorrhage. We believe, therefore, that local venous repair can be recommended in nearly every instance.

Extended venous repairs are clearly more complex and time-consuming procedures, and for patients too unstable to tolerate the increase in operating room time the decision to perform primary venous ligation can be made more liberally. Our data have shown that these repairs have a substantial thrombosis rate (59%) and that limb salvage was not affected by the status of vein repair patency.

Well-documented long-term follow-up will be required before a definitive conclusion can be drawn about the delayed effects of venous interruption. Until these data are available, our group will probably continue to perform even extended venous repair so long as the safety of the patient is not jeopardized.

Computerized Axial Manometry of the Esophagus

A New Method for the Assessment of Antireflux Operations

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This is a presentation of a new manometric parameter of the mechanical competence of the lower esophageal sphincter (LES), the lower esophageal sphincter vector volume (LESVV). It is determined by computer analysis of continuous-pressure measurements during constant speed pullback of a radially oriented 4- 6- or 8-channel manometry catheter across the LES. Patients were studied with this method both before aggressive medical therapy for esophagitis and before and after Nissen fundoplication. LESVV accurately predicted failure of medical therapy and success of the fundoplication. In patients with successful fundoplication, LESVV demonstrated a 100-fold increase in mechanical competence of the LES, even in the absence of increased LES pressure or length, increasing from 113 ± 63 mm^3 to 11357 ± 3733 mm^3.

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SINCE THE FIRST DESCRIPTION of the pressure differential and pressure barrier between the esophagus and stomach by Fyke and co-workers,[1] multiple investigators have attempted to ascribe the normal competence of the lower esophagus and its resistance to reflux from the stomach to this "physiologic lower esophageal sphincter."[2] More recently, it has become obvious that simple measurements of maximal pressures generated in the area of the lower esophagus are insufficient to distinguish between patients who have reflux and those who do not.[3] This discrepancy has relegated esophageal manometry as a surgical investigative tool to an adjunctive position only, in which it was reserved to rule out motility disorders of the esophageal body that might cause symptomatic failures after otherwise perfectly satisfactory antireflux operations.[4] On the other hand, Joelsson et al.[5] have repeatedly emphasized that gastroesophageal reflux is a multifactorial disease and that manometry of the "cardia" or lower esophageal sphincter (LES) is essential to distinguish mechanical failure of that structure from either gastric or esophageal mechanisms that might also cause reflux. Both that group and our own[6,7] have emphasized also that not only is the maximal pressure that the LES can generate important in LES competence, but also that the length over which the LES generates such pressure is of equal importance. These two factors alone, length and pressure, are still insufficient to describe LES mechanical failure, although when taken together, they are much more successful than either one alone.[6]

We postulate that the LES mechanism is not a single "all or none" mechanical structure at the lower end of the esophagus. Rather, it is an aggregation of contractile units, probably corresponding to the muscle fibers of the LES. Any method that describes the LES must take into account not only the length over which those fibers are distributed and the maximum pressure that the strongest of them must generate, but also the symmetry of unit contraction around the circumference of the LES and the distribution of contractile pressures along the entire length of the LES. In a preliminary report we have described a new method, computerized axial manometry

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(CAM), which accomplishes all these interactive measurements.[8] This is a report of the first application of the method to the selection of patients for operation for gastroesophageal reflux.

Methods

CAM was developed in conjunction with the Sensormedics Corporation (formerly Beckman Instruments, Inc.) of Anaheim, California, which markets the hardware and software as the "Esophaplot System." The system consists of a standard four or six lumen motility catheter, composed of 1.0-mm I.D. polyvinyl tubing, with concentric openings either all at the tip or staggered at 3.0 cm proximal from the tip. The individual catheters are perfused at 0.764 mL/min from a custom-made pneumohydraulic pump and connected *via* "T" tubes to standard Statham pressure transducers (Statham Instruments, Oxnard, CA). The transducers are connected to a Sensormedics R-611 8-channel Dynograph (Sensormedics Corp., Anaheim, CA) equipped with a voltage equalizing amplifier to provide linear output to a Texas Instruments Professional Model microcomputer (Sensormedics, Corp.), equipped with 512 KB of RAM and a Winchester 20-MB hard disk. Recorder output is digitized by a Data Translation model 2801 A-D converter in the computer (Sensormedics, Corp.). For LES measurements, the catheter is mechanically pulled back across the LES by a custom-made linear pullback device, powered with a high torque hysteresis synchronous motor, to provide a constant 1.0-cm/sec pullback speed over a wide range of loads. Pressure readings are sampled during pullback from each catheter opening with a 0.4-msec interval between individual catheter readings and a 100-msec interval between sets of readings. Pressure values are therefore concentrically recorded at each millimeter of catheter pullback. Pressure values are recorded in RAM during the examination as 2-byte integer values, and simultaneously displayed graphically on the computer CRT. Seventy seconds of recording is possible, although the maximum required for each pullback rarely approaches 20 seconds.

Subsequently, the RAM recorded values are transferred to disk and converted, by reference to a predetermined standardization curve, to mmHg for final calculations. The Sensormedics system uses a set of programs, written in compiled Microsoft Basic (Stat Systems Inc., Philadelphia, PA), to print out maximum LES pressure relative to intragastric pressure, measured by each catheter tube during a pullback, the length of the LES pressure "hump," and the rate of pressure increase *versus* LES length. The area circumscribed by the LES pressure curve is also calculated as the sum of pressures measured by an individual catheter channel at each millimeter over the length of the LES. A minimum of three pullback measurements is made of the LES for each patient for each examination.

The program also is capable of providing a three-dimensional graphic representation of the LES pressure profile, using the recorded pressures as the individual radii of a three-dimensional figure in which the pressures are plotted at either 90 degrees to each other for a 4-channel catheter, or at 60 degrees to each other for a 6-channel catheter. Individual sets of measurements are spaced 1.0 mm apart in the graphic representation, yielding a three-dimensional figure in which the radius is proportional to the pressure of the LES, oriented around the circumference of the LES. The figure may be rotated around three axes on the computer screen for inspection, especially of LES symmetry.

A final measurement consists of calculation of the volume of the three-dimensional figure, which is a direct representation of the individual force of the LES contractile units, integrated over the length of the LES. This program, written in our laboratories, uses the beginning and end points of the LES as determined above to locate the LES pressure curve in the spectrum of measured values. It then normalizes the values to intragastric pressure as 0 and converts the mv values to mmHg according to the predetermined standardization curve. The area of the individual LES "slices" is then calculated using the LES pressures as radii of the slice. The general formula for the area of an irregular polygon is used:

$$A = 0.5 \times \sin(360/n) \times (P_1P_2 + P_2P_3 + \cdots P_1P_n)$$

where n is the number of catheter channels spaced equidistantly around the circumference of the catheter and P_1 to P_n are the individual pressures measured in the catheter channels. For four pressures, the area of the slice is given by the formula:

$$A = 0.5\,[(P_1 + P_3)(P_2 + P_4)]$$

and for six pressures, by the formula:

$$A = 0.433\,(P_1P_2 + P_2P_3 + P_3P_4 + P_4P_5 + P_5P_6 + P_6P_1),$$

The volume of each "slice" is then calculated by multiplying its area by its thickness, 1.0 mm, and the volume of all the "slices" added to give the volume of the entire LES, the LES vector volume (LESVV). Calculation of this parameter requires approximately 4 seconds of microcomputer time, whereas hand calculation, even if the values were available, would require hours, making it prohibitively expensive for routine clinical use.

Patients

This study has been approved by the Institutional Review Boards of the University of Illinois College of Med-

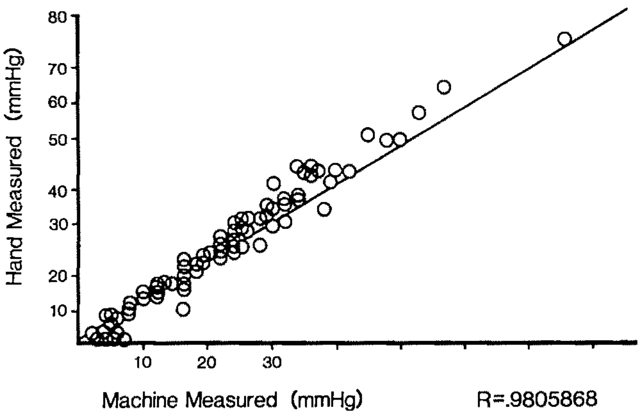

FIG. 1. Scatterplot of hand-measured maximum LES pressures determined by standard manometric means, and the same pressures determined by the on-line microcomputer (r = 0.98).

icine at Chicago, and of Cook County Hospital, Chicago.

Thirty patients were studied. Six patients were normal volunteer controls, and seven patients were studied before they began an eventually unsuccessful course of nonoperative therapy and then again 6 weeks to 3 months after Nissen fundoplication carried out in the "floppy" fashion that we have described.[9] Eight patients were studied before successful nonoperative therapy, and the remaining nine patients were studied after either successful Nissen fundoplication or in the course of investigations for other nonreflux symptoms. In all patients, reflux and/or esophagitis was either confirmed or ruled out by 24-hour pH measurements and esophagoscopy. Patients were unselected and were studied as they were referred to the special Esophageal Disease Clinic of the Division of Surgical Gastroenterology for evaluation and treatment. When matched pair grouping was possible, as in the pre- and postoperative fundoplication group, results were analyzed using the Student's t-test, but, in most cases, only simple variances were calculated since, to be of clinical use, tests must exclude abnormal measurements beyond two standard deviations from the mean.

Results

Initial verification of the measurement method and apparatus is shown in Figure 1. LES pressures measured by standard manual measurement were correlated with those measured by the apparatus in 115 separate determinations. Values correlated with r = 0.98 and significance level of 0.0001. Similar values were obtained for measurement of LES length.

The ability to measure LES maximum pressure, LES length, the area circumscribed by the LES pressure curce, and LESVV to distinguish between patients with proven reflux and those without reflux is shown in Figure 2. When either pressure or length of the LES alone was used, there was a large overlap between the two groups of patients The separation between groups was somewhat better with LES area, and was complete with LESVV.

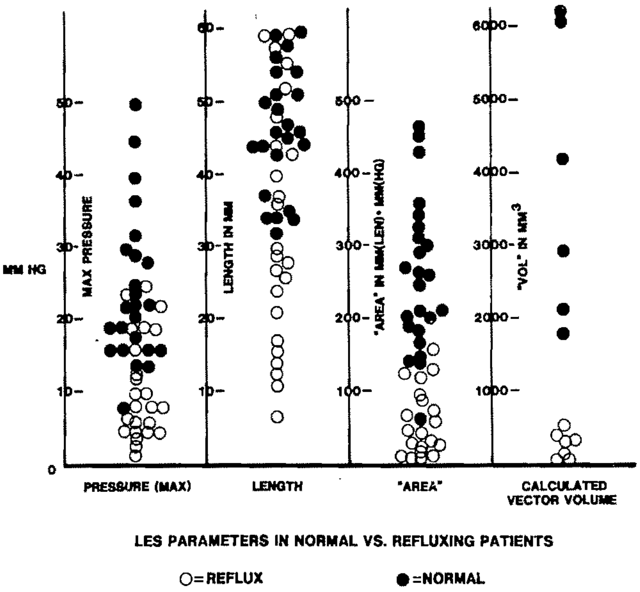

FIG. 2. Distribution of LES maximum pressures (column 1), LES length (column 2), LES area (column 3), and LES volume (column 4) in patients with and without gastroesophageal reflux. Open circles indicate patients with reflux. Filled circles indicate patients without reflux.

Nissen fundoplication had an unpredictable effect on LES maximal pressure (Fig. 3), LES average pressure (Fig. 4), or LES average length (Fig. 5). The effect of LES

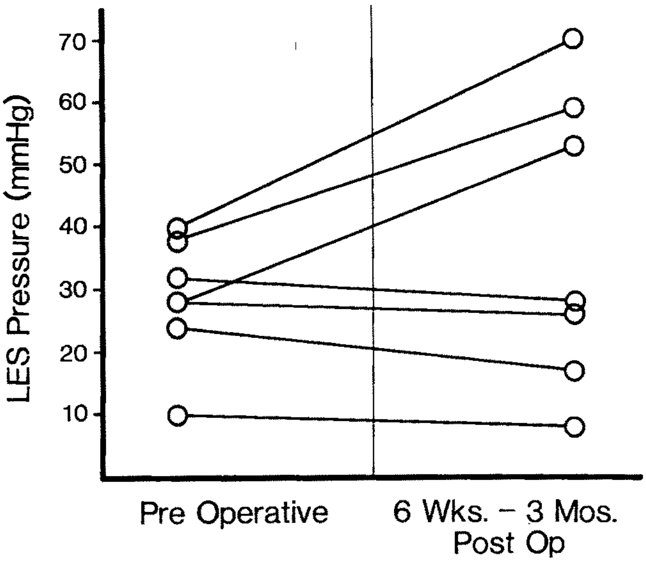

FIG. 3. Maximum LES pressure before and after Nissen fundoplication. Paired measurements in seven patients.

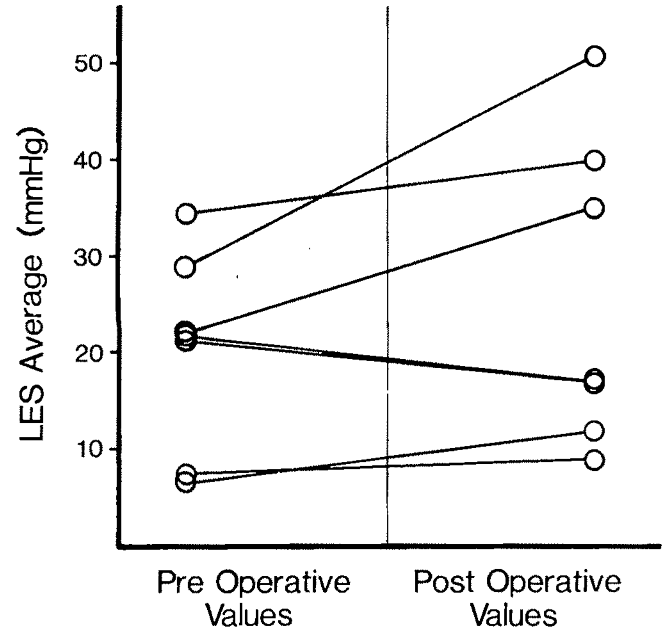

FIG. 4. Averaged LES pressures from a 4-channel manometric catheter before and after Nissen fundoplication. Paired measurements in seven patients.

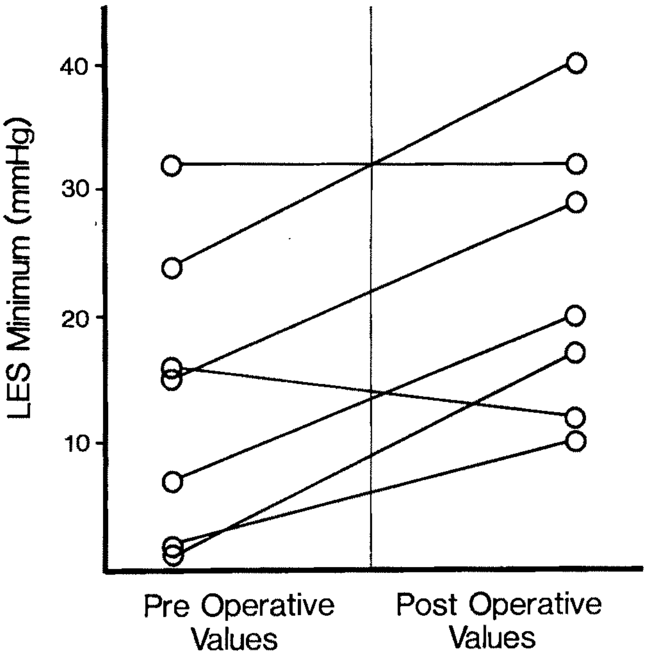

FIG. 6. LES minimum (lowest maximum) pressure before and after Nissen fundoplication. Paired measurements in seven patients.

minimum pressure, the lowest maximum pressure of the four measured in the four-channel catheter on pullback, was more predictable (Fig. 6). In five patients, the pressure was increased by fundoplication, in one patient it was unchanged, and in one patient it decreased. The preoperative value in all patients was 13.9 ± 4.3 mm, and the postoperative value was 22.9 ± 4.2. In the patient with the decrease in minimum pressure, reflux persisted after operation for reasons that are unclear. $LESP_{min}$ for only the patients who were cured of reflux changed from 15.83 ± 4.5 to 25.0 ± 4.27 ($p < 0.05$).

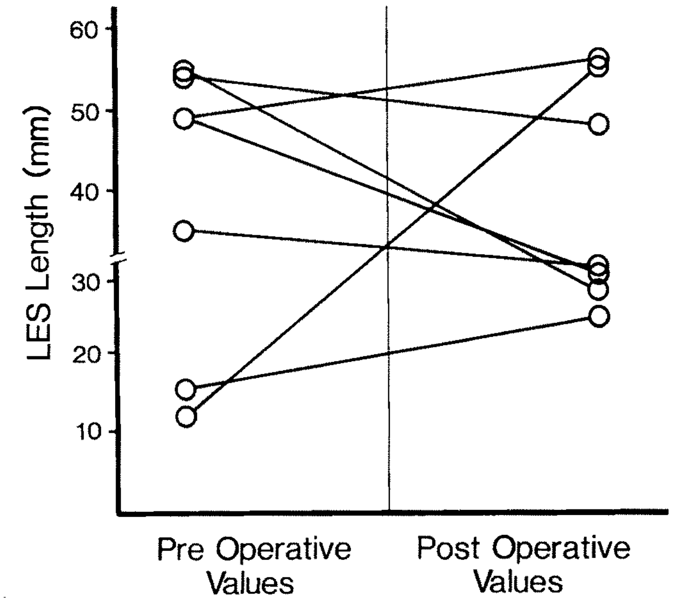

FIG. 5. LES length before and after Nissen fundoplication. Paired measurements in seven patients.

LESVV (Fig. 7) increased greatly after fundoplication in all patients except one, from 119 ± 42 mm^3 to 9994 ± 3508 mm^3 ($p < 0.001$). In the patient with no LESVV increase, the same patient who had the minimum pressure decrease, reflux persisted after fundoplication. All patients except one had very low LESVV values before fundoplication. The patient with the initially high value of 4500 mm^3, had been noncompliant with nonoperative therapy and had only mild esophagitis. He was operated on because he also had severe pulmonary obstructive disease and had nocturnal aspiration.

Figure 8 contains representative printouts of the graphic representations of LESVV from eight different patients, seen in profile. Gastric pressures are on the left end of each figure and esophageal pressures on the right end. As the measuring catheter is drawn from the stomach to the esophagus, from left to right, the pressures measured at millimeter intervals are plotted, in this case as vertical lines, one line per millimeter. That portion of the line extending vertically above the central axis of each figure is proportional to the pressure directed down toward the central axis, and that portion of the line extending vertically down from the central axis represents the pressure directed up toward the central axis. A and B are tracings from control patients. C, D, and E are from patients with reflux, before Nissen fundoplication. In these tracings, the LES is more narrow than controls,

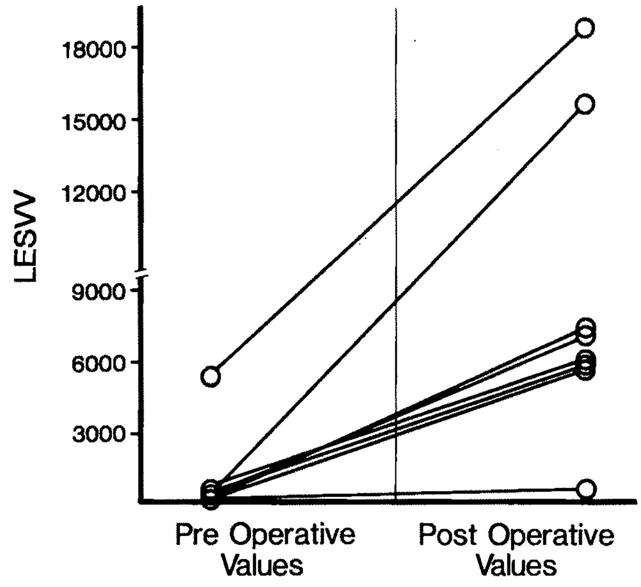

FIG. 7. LES vector volume before and after Nissen fundoplication. Paired measurements in seven patients.

greatly asymmetrical, and in both D and E show absence of one component of the LES profile. F is from the same patient as C, and G is from the same patient as E, after fundoplication. The re-establishment of a more normal LES configuration is obvious. The complete graphic representations plotted on three-dimensional axes show the same changes but are difficult to transpose to the printed page. It can nonetheless be easily appreciated that the volumes of the figures shown in F and G are considerably greater than those in the corresponding preoperative figures in C and E.

The ability of LESVV measurement to predict nonoperative therapy failure and the eventual need for fundoplication is shown in Figure 9. Three groups of patients are plotted: those without reflux for comparison with those with reflux who were successfully treated medically and those who failed medical therapy either because it was ineffective or because they could not tolerate the rigorous treatment necessary to control their reflux. There are 11 patients in the group who eventually required operation, which includes four patients who have not yet been studied after operation. All of those patients had LESVV values below 1000 mm^3 with a mean of 161 ± 72 mm^3, and a 95% confidence range of 0–639 mm^3. The patient who was unable to comply with nonoperative management is excluded from this group because he was never adequately treated with medical measures. There are seven patients in the group who succeeded with nonoperative therapy and who could decrease or cease treatment entirely after resolution of esophagitis. Mean LESVV in that group was 1582 ± 159 mm^3 with a 95% confidence range of 740–2424 mm^3. Some minimal overlap was noted between that group and the control group, which was included for comparison.

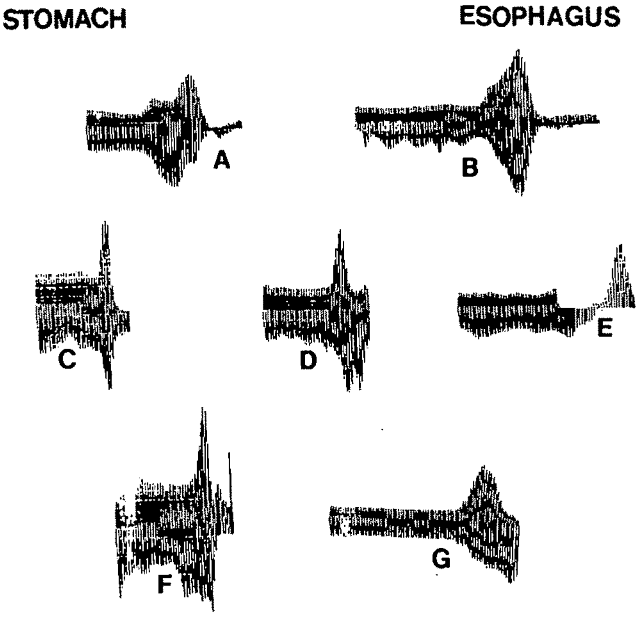

FIG. 8. Manometric pressure profile graphs, in two dimensions of LES pressures measured at 1-mm intervals across the LES from the stomach to the esophagus. A, B: normal controls. C, D, E: patients with reflux. F, G: patients after fundoplication.

Dose LESVV reflect the severity of gastroesophageal reflux as determined by 24-hour pH measurements, or the severity of the patient's peptic esophagitis graded endoscopically? LESVV was correlated with 24-hour pH measurements in patients with endoscopically demonstrated esophagitis. The percentage of the 24-hour

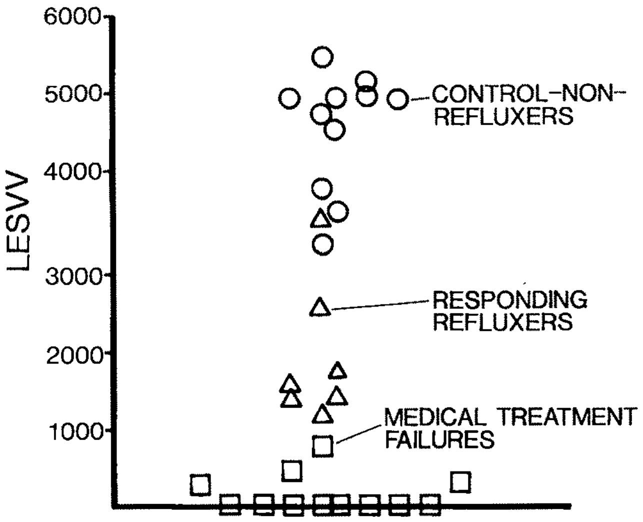

FIG. 9. Distribution of control patients (circles), patients with reflux who were cured by nonoperative treatment (triangles), and patients who eventually required operation (medical failures) (squares), according to pretreatment LESVV values.

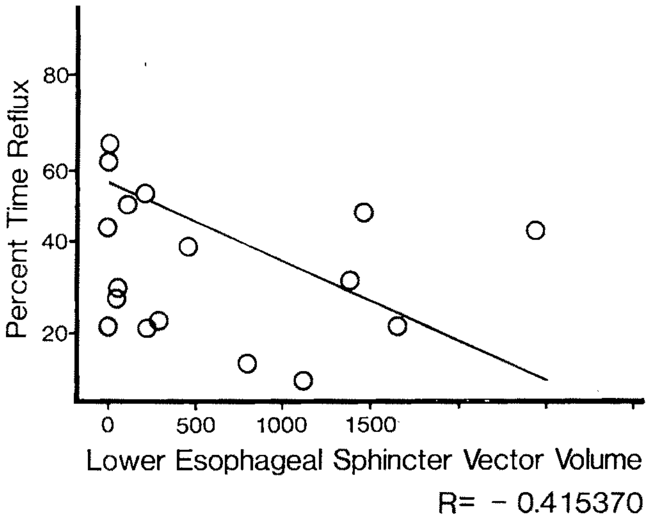

FIG. 10. Scatterplot LESVV *versus* the total percentage of a 24-hour period that the patient's intraesophageal pH 5.0 cm above the LES was les than 4.0.

measurement period that the patient's intraesophageal pH was below 4.0 *versus* LESVV in that patient is shown in Figure 10. Approximately the same results were obtained when the percentage of upright reflux time was used instead of total time. As demonstrated, there was insignificant correlation (r = −0.40) between the measured volume of reflux and LESVV. As might be expected from this finding, there was also insignificant correlation between this measure of the severity of reflux and whether the patient would eventually require operation.

There was similar lack of correlation between LESVV and the endoscopic severity of the patient's esophagitis.

Discussion

Computerized esophageal motility data are not new. Castell and others[10–12] have used large mini- or mainframe computers for both collection and interpretation of motility data in the body of the esophagus and for prolonged measurement of reflux. The significant new method proposed here is the application of the microcomputer to real-time, on-line data collection and analysis and the introduction of a new parameter for measurement of LES mechanical integrity, the LESVV. A preliminary report of the method has been presented.[8] Castell and Castell have recently presented a similar method with a different but equally reliable microcomputer system, for determination of all parameters discussed here except for LESVV.[13]

Physiologic mechanisms that prevent gastroesophageal reflux remain incompletely understood although currently it is recognized that the central barrier to reflux prevention is the lower esophageal sphincter mechanism. Much confusion has been generated by the erroneous assumption that reflux necessarily causes esophagitis and that the absence of esophagitis, regardless of other symptoms, rules out reflux. In this study, we have avoided that problem simply by excluding patients with reflux but without esophagitis.

A current theory that is widely held is that all reflux, normal as well as pathologic, occurs as a result of transient LES relaxation.[14] On the other hand, it is well known also that, on balance, maximal LES pressure is decreased, especially in patients with reflux so intransigent as to require surgical therapy. DeMeester and coworkers have called such a condition "mechanical LES failure"[15] and used it as an indication for an LES protective operation such as a Nissen fundoplication. The purpose of this study was to further refine the definition of mechanical LES failure, beyond simple LES shortening, simple LES pressure decreases, or combinations of the two.

Any measure of the static, mechanical LES pressure barrier must provide some measure of the functional capacity of the entire LES msucle mass. It is a matter of common intuition that the resistance of the LES to backflow must be the sum of the resistances provided by all the circular muscle fibers that make up the LES. This is analogous to the concept of series electrical resistance to current flow, in which the total resistance of the electrical circuit, made up of resistors connected end to end (in series), is the sum of the individual resistor resistance values. The LES may be thought of as such a "series resistance circuit." Although the single highest resistance in the circuit is provided by the point at which the LES exerts its highest or maximal pressure, total resistance to backflow is also made up of the remaining points along LES length at which lesser pressures are generated. A major advance in the application of this hypothesis to the LES was made by the addition of LES total length to simple maximum pressure.[6] This introduced the concept that LES backflow resistance is generated over the length of the LES and not at a single point at which the maximum pressure is measured. That the concept is valid is demonstrated in the first series of patient measurements in this study. Neither simple pressure measurements nor simple length measurements adequately separate patients with reflux from those without reflux. LES area measurements in which pressure is continuously measured over the length of the LES provide much better separation. Nonetheless, LES area measurement has the major drawback in that it is made in one plane only, ignoring the fact that the LES must exert its pressure not only over its length but also around its circumference. Winans[16] has shown that the LES does not contract symmetrically around its circumference; therefore, the assumption that measured pressures at any given LES level are equally exerted from all points around the LES is invalid. The difference in pressures registered by multiple concentrically oriented catheters at any single level in the LES is caused by this asymmetry.

It is easily demonstrated by simple calculus that pressure exerted toward the center of a cylinder from around its circumference is the sum of the centrally directed pressure vectors measured at infinitely small intervals around the circumference of the cylinder. If the radius of the cylinder is directly proportional to those pressure vectors, then the centrally directed pressure, which generates cylinder "closure" at that point, will be directly proportional to the area of the cylinder at that point. The detailed mathematical demonstration of this phenomenon is not appropriate to this discussion. Total resistance to flow through the cylinder will then be directly proportional to the sum of the cross-sectional areas, measured at infinitely small intervals along the length of the cylinder.

Physical limitations of the size of the pressure measurement device that can be passed through the LES without unduly distending it limit the number of radially oriented pressure measurements that can be made at a single point to six or eight at the most. In this study, we used four pressure channels but have subsequently begun to use six for the greater definition afforded. It was likewise impossible to measure pressures at infinitely small intervals along LES length, but it is a common observation that pressure changes from millimeter to millimeter are very small compared with the absolute magnitude of radially measured pressure. Accordingly, areas were measured at each millimeter, both because more frequent measurements would detect minimal change and because of the finite sampling rate of which the A-D interface was capable. Because pressure measurements are taken axially and then both recorded and calculated by computer, we have called the method computerized axial manometry or CAM. Since the sum of cross-sectional areas of a cylinder taken along its length equals the volume of the cylinder, we have called the resultant "volume" of the LES the LES vector volume, or LESVV.

Using this new manometric parameter, we have studied two groups of patients, one with reflux before and after Nissen fundoplication, and a larger one with reflux, at first treated by standard nonoperative methods, and then with treatment failures submitted to Nissen fundoplication.

In the first group, "floppy" Nissen fundoplication did not change either LES maximum pressure, LES average pressure, or LES length, despite stopping reflux in all patients but one. The failure of this variant of the Nissen fundoplication to augment LES maximum pressure has been reported elsewhere and is suggested as the reason that the "floppy Nissen" avoids the gas bloat syndrome.[17]

LES minimum pressure, the lowest of the four radially oriented pressures, was increased in five patients, unchanged in one patient, and decreased in one patient. The patient with the decreased value had persistent reflux. This suggests that one action of the Nissen fundoplication was to make the LES more symmetrical around its circumference, and also that the procedure had corrected the "weak link in the chain."

An approximate 80-fold increase was produced in LESVV by fundoplication, demonstrating that the operation, even without dramatic increases in single maximum pressure measurements or LES length, greatly increased the total antireflux barrier. All patients except one had abrupt cessation of reflux and reflux symptoms. If that patient is excluded, then LESVV increased 100-fold in those patients who were cured of reflux. It is evident that for LESVV to increase by these magnitudes, pressure, length, or symmetry must be increased. Individual patients had such increases in one or more of these parameters, but no single parameter, with the possible exception of $LESP_{min}$, changed in the same direction for all patients. In addition, the "shape" of the LESVV graphic representation of the LES changed. Pressures along the length of the LES were increased without exceeding LES maximum pressure, but still greatly contributing to the new pressure barrier.

In the second group of patients, pretreatment LESVV determinations provided clear separation between those patients who succeeded with nonoperative therapy and those who eventually required operation despite adequate treatment. Although it has been suggested that LES maximum pressures less than 6.0 mmHg or very severe grades of reflux esophagitis are indications for immediate operation,[18] LESVV seems to provide the most clear definition to date. It is a direct measure of the mechanical competence of the LES, and it is this alone that is corrected by operations for reflux. That LESVV correlated neither with the duration of reflux as measured by 24-hour pH studies nor with the grade of esophagitis determined endoscopically is not surprising. Reflux duration depends on the availability of material to be refluxed, which is, in turn, dependent on diet, exercise, and other factors. The degree of esophagitis depends on the composition of the material that is refluxed, how long it remains in contact with the esophagus, and whether the esophagus is sensitive to it.

The ability of LESVV to distinguish reflux patients who will require operation from those who will not is of importance both for the comfort of the patient, who no longer will have to persevere through a trial of ultimately unsuccessful therapy, and as a cost saving measure in the treatment of this common disease. A few patients will also have more severe complications of reflux develop during impotent nonoperative treatment, and these can be avoided by earlier operation.

It is now appropriate to change the recommendation for the place of manometry in the evaluation and treatment of gastroesophageal reflux disease. CAM should be used in the evaluation of the 10% of patients who have failed simple mechanical measures for reflux prevention and who are considered for more vigorous and aggressive medical treatment. In these patients, it will allow the identification of those patients in whom such treatment will prove fruitless and bring them to an early and effective operation.

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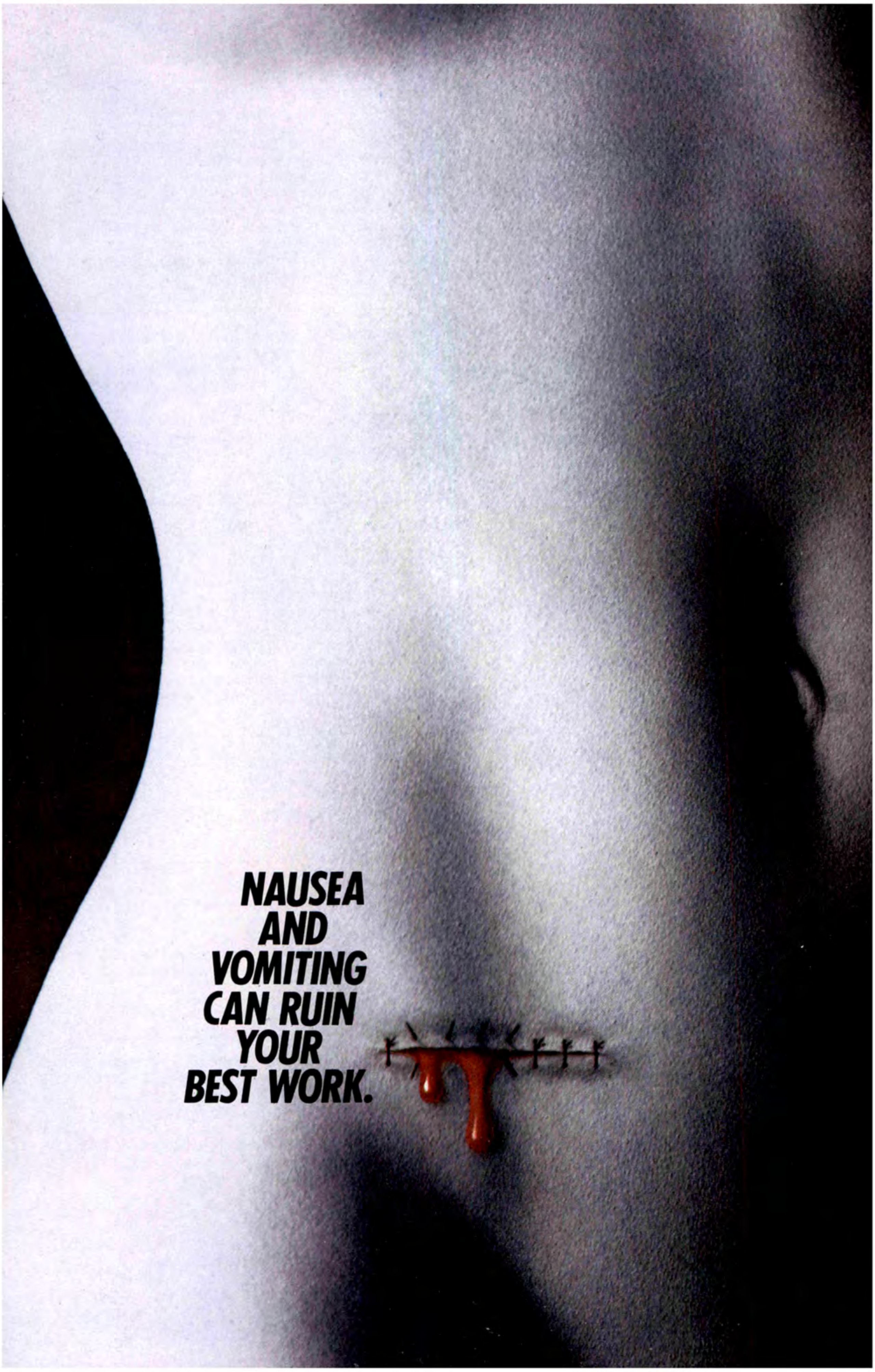
Continued on page 32A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(butorphanol tartrate)

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BRISTOL®

Stadol® (butorphanol tartrate)
Brief Summary of Prescribing Information

For complete information, consult Official Package Circular.

INDICATIONS AND USAGE–Stadol is recommended for the relief of moderate to severe pain. Stadol can also be used for preoperative or preanesthetic medication, as a supplement to balanced anesthesia, and for the relief of prepartum pain.

CONTRAINDICATIONS–Stadol should not be administered to patients who have been shown to be hypersensitive to it.

WARNINGS–Patients Physically Dependent on Narcotics: Because of its antagonist properties, Stadol is not recommended for patients physically dependent on narcotics. Detoxification in such patients is required prior to use.

Due to the difficulty in assessing addiction in patients who have recently received substantial amounts of narcotic medication, caution should be used in the administration of Stadol. Detoxification of such patients prior to usage should be carefully considered.

Use During Balanced Anesthesia: Since the combined respiratory depressant effect of all intravenous medication used during conduct of general anesthesia may lead to underventilation or apnea, butorphanol should be administered during balanced anesthesia only by persons specifically trained in the use of intravenous anesthetics and adjuncts, the maintenance of a patent airway and management of respiratory effects of all intravenous medication administered. An opioid antagonist, resuscitative and intubation equipment and oxygen should be readily available.

Drug Dependence: Special care should be exercised in administering Stadol to emotionally unstable patients and to those with a history of drug misuse. When long term therapy is contemplated, such patients should be closely supervised. Even though Stadol has a low physical dependence liability, care should be taken that individuals who may be prone to drug abuse are closely supervised. It is important to avoid increases in dose and frequency of injections by the patient and to prevent the use of the drug in anticipation of pain rather than for the relief of pain.

Head Injury and Increased Intracranial Pressure: Although there is no clinical experience in patients with head injury, it can be assumed that Stadol, like other potent analgesics, elevates cerebrospinal fluid pressure. Therefore the use of Stadol in cases of head injury can produce effects (e.g., miosis) which may obscure the clinical course of patients with head injuries. In such patients Stadol must be used with extreme caution and only if its use is deemed essential.

Cardiovascular Effects: Because Stadol increases the work of the heart, especially the pulmonary circuit, (see Clinical Pharmacology), the use of this drug in acute myocardial infarction or in cardiac patients with ventricular dysfunction or coronary insufficiency should be limited to those who are hypersensitive to morphine sulfate or meperidine.

PRECAUTIONS–Certain Respiratory Conditions: Because Stadol causes some respiratory depression, it should be administered only with caution and low dosage to patients with respiratory depression (e.g., from other medication, uremia, or severe infection), severely limited respiratory reserve, bronchial asthma, obstructive respiratory conditions, or cyanosis.

Impaired Renal or Hepatic Function: Although laboratory tests have not indicated that Stadol causes or increases renal or hepatic impairment, the drug should be administered with caution to patients with such impairment. Extensive liver disease may predispose to greater side effects and greater activity from the usual clinical dose, possibly the result of decreased metabolism of the drug by the liver.

Biliary Surgery: Clinical studies have not been done to establish the safety of Stadol administration to patients about to undergo surgery of the biliary tract.

Usage as a Pre-operative or Pre-anesthetic Medication: Slight increases in systolic blood pressure may occur, therefore caution should be employed when Stadol is used in the hypertensive patient.

Usage in Pregnancy: The safety of Stadol for use in pregnancy prior to the labor period has not been established; therefore, this drug should be used in pregnant patients only when in the judgment of the physician its use is deemed essential to the welfare of the patient.

Reproduction studies have been performed in rats, mice, and rabbits and have revealed no evidence of impaired fertility or harm to the fetus due to Stadol at about 2.5 to 5 times the human dose.

Usage in Labor and Delivery: Safety to the mother and fetus following the administration of Stadol during labor has been established. Patients receiving Stadol during labor have experienced no adverse effects other than those observed with commonly used analgesics. Stadol should be used with caution in women delivering premature infants.

Usage in Nursing Mothers: The use of Stadol in lactating mothers who are nursing their infants is not recommended, since it is not known whether this drug is excreted in milk. Stadol has been used safely for labor pain in mothers who subsequently nursed their infants.

Usage in Children: Safety and efficacy in children below age 18 years have not been established at present.

ADVERSE REACTIONS–The most frequent adverse reactions in 1250 patients treated with Stadol are: sedation (503, 40%), nausea (82, 6%), clammy/sweating (76, 6%).

Less frequent reactions are: headache (35, 3%), vertigo (33, 3%), floating feeling (33, 3%), dizziness (23, 2%), lethargy (19, 2%), confusion (15, 1%), lightheadedness (12, 1%).

Other adverse reactions which may occur (reported incidence of less than 1%) are:

CNS: nervousness, unusual dreams, agitation, euphoria, hallucinations, seizures
Autonomic: flushing and warmth, dry mouth, sensitivity to cold
Cardiovascular: palpitation, increase or decrease of blood pressure
Gastrointestinal: vomiting
Respiratory: slowing of respiration, shallow breathing
Dermatological: rash or hives
Eye: diplopia or blurred vision

OVERDOSAGE–Manifestations: Although there have been no experiences of overdosage with Stadol during clinical trials, this may occur due to accidental or intentional misuse as well as therapeutic use. Based on the pharmacology of Stadol, overdosage could produce some degree of respiratory depression and variable cardiovascular and central nervous system effects.

Treatment: The immediate treatment of suspected Stadol overdosage is intravenous naloxone. The respiratory and cardiac status of the patient should be evaluated constantly and appropriate supportive measures instituted, such as oxygen, intravenous fluids, vasopressors and assisted or controlled respiration.

SUPPLY–Stadol (butorphanol tartrate) Injection for I.M. or I.V. use is available as follows:

NDC 0015-5644-20–2 mg per ml, 2-ml vial
NDC 0015-5645-20–1 mg per ml, 1-ml vial
NDC 0015-5646-20–2 mg per ml, 1-ml vial
NDC 0015-5648-20–2 mg per ml, 10-ml multi-dose vial

For information on package sizes available, refer to the current price schedule.

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Surgeon for Oncology Clinic and Hospital: BC/BE General Surgeon, Salary negotiable. Send CV to: **P.O. Box 35161, Dallas, Texas 75235.**

THORACIC/GENERAL SURGEON— Thoracic/General Surgeon with experience in pulmonary surgery and thoracic trauma to join 34 physician multi-specialty clinic. Potential vascular work. Two established Pulmonologists on staff. Must be Board Certified or eligible. 100 miles southeast of St. Louis. Population 28,000 plus 25,000 Southern Illinois University students. Drawing area near 100,000. Flexible compensation package with generous fringe benefits including health and disability insurance, vacation, CME leave, and profit sharing retirement plan. Fee-for-service plus prepaid. Contact: **Bill Harris, Administrator; Carbondale Clinic, S.C.; 2601 West Main Street, Carbondale, IL 62901 or call (618) 549-5361.**

THORACIC SURGERY— Well established Group in suburban New York area is seeking a Board Certified/Board Eligible university trained associate to provide quality General/Thoracic/PV Surgery (no open heart). Excellent salary and benefits leading to partnership. Malpractice paid. Send CV to **Box ANN10A, J. B. Lippincott Company, Philadelphia, PA 19105.**

The Center for Clinical Medical Ethics (CCME) at the University of Chicago is pleased to announce **The National Leadership Training Program for Physicians in Clinical Medical Ethics.** This new training opportunity will prepare mid-career physicians as leaders of programs in clinical medical ethics. Training will include one year at the CCME with stipend of $52,000, followed by three years at the trainee's sponsoring institution with program support of $15,000/year. The Center seeks nominations from deans of medical schools and from directors of major health organizations and ethics institutes. CEOs of major health systems may also nominate an individual but the health system must support the entire cost of training. Sponsoring institution must be committed to the development of a clinical ethics program. The University of Chicago is an Affirmative Action/Equal Opportunity Employer. Please direct requests for applications and inquiries to **Dr. Mark Siegler, CCME, Box 72, 5841 S. Maryland Ave., Chicago, IL 60637, (312) 702-1453.**

Continued on page 34A

INTRODUCING

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IN ACID SUPPRESSION

100 ml
NDC 0173 0407 00
Zantac® Injection Premixed
(ranitidine hydrochloride)
50 mg
50 mg/100 ml in 0.45% sodium chloride
Sterile, single-dose flexible plastic container
Nonpyrogenic. Contains no preservative
See package insert.
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dium chloride 450 mg; and citric acid 30 mg and dibasic
odium phosphate 180 mg as buffers in water for injection.
80 mOsm/liter (approx.); pH 6.7 to 7.3. Additives should
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tainer is undamaged. Must not be used in series connecti
98-1932-2/R-2 592802
Manufactured for Glaxo Inc.,
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Convenient

☐ Ready to use–no mixing needed

☐ Premixed 100-ml bag, containing 50 mg ranitidine (as the hydrochloride)

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Raises gastric pH in critical care patients for up to 8 hours*

No significant drug interactions with the hepatic P-450 enzyme system at recommended doses

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Zantac® Injection Premixed
ranitidine HCl/Glaxo

New premixed 100-ml bag containing 50 mg ranitidine HCl

*Some patients may require q6h dosing.

See next page for brief summary of Product Information.

Glaxo/ROCHE

ZANTAC® Injection
(ranitidine hydrochloride)

ZANTAC® Injection Premixed
(ranitidine hydrochloride)

The following is a brief summary only. Before prescribing, see complete prescribing information in ZANTAC® Injection/ZANTAC® Injection Premixed product labeling.
INDICATIONS AND USAGE: ZANTAC® Injection and ZANTAC® Injection Premixed are indicated in some hospitalized patients with pathological hypersecretory conditions or intractable duodenal ulcers, or as an alternative to the oral dosage form for short-term use in patients who are unable to take oral medication.
CONTRAINDICATIONS: ZANTAC® Injection and ZANTAC® Injection Premixed are contraindicated for patients known to have hypersensitivity to the drug.
PRECAUTIONS: General: 1. Symptomatic response to ZANTAC® therapy does not preclude the presence of gastric malignancy.
2. Since ZANTAC is excreted primarily by the kidney, dosage should be adjusted in patients with impaired renal function (see **DOSAGE AND ADMINISTRATION**). Caution should be observed in patients with hepatic dysfunction since ZANTAC is metabolized in the liver.
3. In controlled studies in normal volunteers, elevations in SGPT have been observed when H_2-antagonists have been administered intravenously at greater than recommended doses for five days or longer. Therefore, it seems prudent in patients receiving IV ranitidine at doses greater than or equal to 100 mg qid for periods of five days or longer to monitor SGPT daily (from day 5) for the remainder of IV therapy.
Laboratory Tests: False-positive tests for urine protein with Multistix® may occur during ZANTAC therapy, and therefore testing with sulfosalicylic acid is recommended.
Drug Interactions: Although ZANTAC has been reported to bind weakly to cytochrome P-450 in vitro, recommended doses of the drug do not inhibit the action of the cytochrome P-450-linked oxygenase enzymes in the liver. However, there have been isolated reports of drug interactions that suggest that ZANTAC may affect the bioavailability of certain drugs by some mechanism as yet unidentified (eg, a pH-dependent effect on absorption or a change in volume of distribution).
Pregnancy: ***Teratogenic Effects: Pregnancy Category B:*** Reproduction studies have been performed in rats and rabbits at oral doses up to 160 times the human oral dose and have revealed no evidence of impaired fertility or harm to the fetus due to ZANTAC. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.
Nursing Mothers: ZANTAC is secreted in human milk. Caution should be exercised when ZANTAC is administered to a nursing mother.
Pediatric Use: Safety and effectiveness in children have not been established.
ADVERSE REACTIONS: Transient pain at the site of intramuscular injection has been reported. Transient local burning or itching has been reported with intravenous administration of ZANTAC® Headache, sometimes severe, seems to be related to ZANTAC administration. Constipation, diarrhea, nausea/vomiting, and abdominal discomfort/pain have been reported. There have been rare reports of malaise, dizziness, somnolence, insomnia, vertigo, tachycardia, bradycardia, premature ventricular beats, and arthralgias. Rare cases of reversible mental confusion, agitation, depression, and hallucinations have been reported, predominantly in severely ill elderly patients. Rare cases of reversible blurred vision suggestive of a change in accommodation have been reported.

In normal volunteers, SGPT values were increased to at least twice the pretreatment levels in 6 of 12 subjects receiving 100 mg qid IV for seven days, and in 4 of 24 subjects receiving 50 mg qid for five days. With oral administration there have been occasional reports of reversible hepatitis, hepatocellular or hepatocanalicular or mixed, with or without jaundice.

Reversible blood count changes (leukopenia, granulocytopenia, and thrombocytopenia) have occurred in a few patients. Rare cases of agranulocytosis or of pancytopenia, sometimes with marrow hypoplasia, have been reported.

Although controlled studies have shown no antiandrogenic activity, occasional cases of gynecomastia, impotence, and loss of libido have been reported in male patients receiving ZANTAC, but the incidence did not differ from that in the general population.

Incidents of rash, including rare cases suggestive of mild erythema multiforme, and, rarely, alopecia, have been reported, as well as rare cases of hypersensitivity reactions (eg, bronchospasm, fever, rash, eosinophilia) and small increases in serum creatinine.
OVERDOSAGE: Information concerning possible overdosage and its treatment appears in the full prescribing information.
DOSAGE AND ADMINISTRATION: (See complete prescribing information in ZANTAC® Injection/ZANTAC® Injection Premixed product labeling.)
Dosage Adjustment for Patients with Impaired Renal Function: On the basis of experience with a group of subjects with severely impaired renal function treated with ZANTAC, the recommended dosage in patients with a creatinine clearance less than 50 ml/min is 50 mg every 18 to 24 hours. Should the patient's condition require, the frequency of dosing may be increased to every 12 hours or even further with caution. Hemodialysis reduces the level of circulating ranitidine. Ideally, the dosage schedule should be adjusted so that the timing of a scheduled dose coincides with the end of hemodialysis.
HOW SUPPLIED: ZANTAC® Injection, 25 mg/ml, containing phenol 0.5% as preservative is available as follows:
(NDC 0173-0362-38) 2-ml single-dose vials (Tray of 10)
(NDC 0173-0363-39) 10-ml multidose vials (Singles)

Store below 30°C (86°F). Protect from light.

ZANTAC® Injection Premixed in 0.45% Sodium Chloride, 0.5 mg/ml, is available as a sterile premixed solution for IV administration in 100-ml single-dose flexible plastic containers (NDC 0173-0407-00). It contains no preservatives.

Exposure of pharmaceutical products to heat should be minimized. Avoid excessive heat. Protect from freezing. It is recommended that the product be stored at room temperature (25°C); however, brief exposure up to 40°C does not adversely affect the product.

Glaxo

ZANTAC® Injection in vials:
Glaxo Inc., Research Triangle Park, NC 27709
ZANTAC® Injection in prefilled syringes:
Manufactured for Glaxo Inc., Research Triangle Park, NC 27709
by Survival Technology, Inc., St. Louis, MO 63144
ZANTAC® Injection Premixed:
Manufactured for Glaxo Inc., Research Triangle Park, NC 27709
by Abbott Laboratories, North Chicago, IL 60064
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Continued from page 32A

The community of **ARTESIA, NEW MEXICO** is seeking a Board Certified or Eligible GENERAL SURGEON to establish a private practice. Fully-equipped office with established referral patterns available for purchase. Community-based financial assistance may be available to the right individual. Artesia is a community of 14,000 located in Southeast New Mexico. A great place to raise a family—peaceful community with year-round recreation and excellent weather. Fully equipped, 38-bed new hospital. Please submit CV to: **Bill Norris, Southwest Community Health Services, P.O. Box 26666, Albuquerque, NM 87125-6666; or, call 1-800-545-4030, Ext. 8300.**

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VASCULAR SURGEON— The Department of Surgery, Medical College of Pennsylvania is recruiting a board certified/eligible vascular surgeon for a full-time academic position. Responsibilities include patient care, research, medical student and resident instruction. Benefits and insurance included. **Apply to Division of Vascular Surgery, Medical College of Pennsylvania, Philadelphia, PA 19129.**

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Qualified candidates must be board eligible or certified in general surgery and eligible/certified in surgical critical care. Training and experience in the care of trauma and critical care patients a must. Interested applicants send resumes to:

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Gastroplasty and Fundoplication for Complex Reflux Problems

Long-term Results

F. GRIFFITH PEARSON, M.D., F.R.C.S.(C.), JOEL D. COOPER, M.D., F.R.C.S.(C.),
G. ALEXANDER PATTERSON, M.D., F.R.C.S.(C.), JUAN RAMIREZ, M.D., and THOMAS R. TODD, M.D., F.R.C.S.(C.)

Between 1964 and 1984, 430 patients with complex reflux problems were managed by a modified Collis gastroplasty and partial fundoplication. The indications for selecting the addition of gastroplasty were as follows: (1) obvious acquired shortening due to peptic esophagitis and stricture, and (2) subtler degrees of acquired shortening frequently encountered in cases that required reoperation and in patients with massive sliding hiatal hernia. The addition of gastroplasty in this second group obviates the risk of even minimal tension on the repair. Follow-up is complete in 382 patients (90%), and extends 1–20 years. Two hundred fifty patients have been followed up for 5 or more years and 101 patients for more than 10 years. Results were classified as follows: good: asymptomatic, or inconsequential symptoms requiring no therapy; fair: improved, but with symptoms and/or endoscopic findings requiring intermittent therapy; poor: unimproved or worse. Patients are divided into four categories, and the results are tabulated below (see Table 2). The best results are obtained in patients with acquired shortening due to esophagitis with and without stricture who have had no prior antireflux surgery and have no associated primary motor disorder. The proportion of unsatisfactory results is almost tripled (20% fair or poor) after reoperation after one or more failed antireflux procedures. When reflux esophagitis and stricture are associated with a primary motor disorder, onl half of the patients have a good result sustained throughout long-term follow-up.

THE CURRENT REPORT reviews the experience with a group of patients with complex reflux problems managed by a modified Collis gastroplasty[1] combined with a Belsey-type partial fundoplication. We first reported our early experience with this procedure in 1971.[2] A meaningful evaluation of results requires a long follow-up and is particularly important for the assessment of surgery for benign disease in which a majority of patients survive for long periods.

From the Division of Thoracic Surgery, University of Toronto, and Toronto General Hospital, Toronto, Ontario, Canada

This procedure was initially designed for the management of patients with sequelae of grades of peptic esophagitis resulting in acquired shortening. During the first few years, the operation was restricted to patients with peptic strictures associated with obvious acquired shortening. A Belsey Mark IV repair was our procedure of choice in the absence of obvious acquired shortening. With experience, however, it became apparent that subtle degrees of shortening occurred in many cases of gross ulcerative esophagitis, even without a peptic stricture. On occasion, this resulted in tension on a standard Belsey repair that was evident only after the operation had been completed. Similar difficulty is unpredictably encountered in patients who have repeat antireflux operations. Since the distal esophagus is already scarred from previous surgery we have chosen to add a gastroplasty to the fundoplication in almost all such reoperations to obviate any possibility of tension on the antireflux reconstruction. Similar subtle degrees of acquired shortening are commonly encountered in patients with the most advanced stages of sliding hiatus hernia in which most of the stomach lies in the posterior mediastinum and has usually undergone organoaxial volvulus. Many patients have little or no symptomatic reflux at the time of presentation with an intrathoracic stomach. A careful history, however, will reveal that most of these patients have had significant symptomatic reflux during the years preceding this late stage,[3] and a degree of tension is commonly encountered when a standard Belsey repair is used. Like Belsey,[4] we observed a higher than expected recurrence rate when these cases of intrathoracic stomach were assessed over a longer follow-up period. As a result of these observations, we have been adding a gas-

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Presented at the 107th Annual Meeting of The American Surgical Association, Palm Beach, Florida, April 21–23, 1987.

Reprint requests: Dr. F. G. Pearson, Bell Wing 1-636, Toronto General Hospital, Toronto, Ontario, Canada M5G 2C4.

Submitted for publication: April 24, 1987.

troplasty to the fundoplication during the past 15 years. Patients with a true paraesophageal hernia are excluded from this approach.

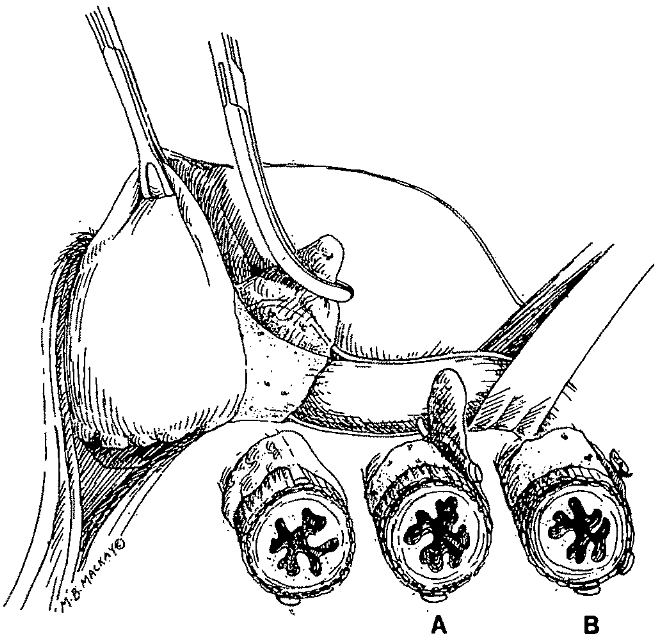

FIG. 1. The esophagogastric fat pad is always present and envelops the esophagogastric junction (A). This fat pad is meticulously dissected from most of the circumference of the junction. With this dissection, the left vagus nerve is lifted free from the muscular wall of the esophagus and is carried with the fat pad (B). The fatty tissue is cleared away from the entire anterior surface of the esophagogastric junction and adjacent upper part of the lesser curvature. This dissection is tedious and requires coagulation or ligation of many small penetrating vessels similar to the technique for highly selective vagotomy. The gastroplasty tube can then be constructed through an area of stomach that is free of any fatty covering. This dissection results in displacement of the left vagus nerve to a more posterior location where it lies close to the right vagus nerve (C).

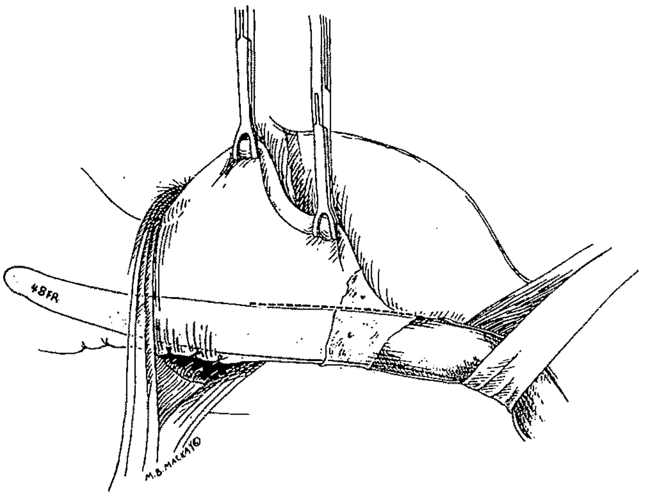

FIG. 2. A No. 48 French Maloney bougie is passed *via* the mouth through the esophagus and well into the stomach beyond. The dotted line indicates the site of division of the gastric wall in order to create a gastric tube in continuity with the distal esophagus.

Material and Methods

Between 1964 and 1984, 430 patients had modified gastroplasty and partial fundoplication for the management of complex reflux problems. Ages ranges between 19 and 79 years with a mean age of 56 years.

Operative Technique

A double lumen orotracheal tube or bronchus blocker is used in each case to permit collapse of the left lung during the procedure. Exposure is obtained through the sixth, left intercostal space. The esophagus is mobilized circumferentially from the hiatal attachments below to the back of the pulmonary hilum above. The greater and lesser peritoneal sacs are opened through the hiatus and the upper part of the gastrohepatic omentum is divided to allow the cardia to be freely elevated into the left hemithorax. In patients who have repeat antireflux surgery, this part of the operation may require additional abdominal exposure obtained through a marginal incision in the anterior aspect of the left diaphragm, in its muscular part near the costal margin. The esophagogastric fat pad is meticulously dissected free (see Fig. 1). Up to this point, the operation is identical to that described by Belsey for his Mark IV repair. The addition of gastroplasty requires a more extensive clearance of the esophagogastric fat pad from the anterior and lesser curvature aspects of the cadia (see Fig. 2). The gastric tube is created on the lesser curvature side of the stomach, in continuity with the distal esophagus for a length of 4–5 cm. This is usually accomplished with a single application of the GIA stapler. Traction is exerted on the greater curvature side of the gastric fundus before closing the jaws of the stapler to ensure that the gastric tube closely approximates the diameter of an indwelling No. 48 French Maloney bougie. The gastric tube should be of uniform diameter throughout its length (see Figs. 3 and 4). The subsequent 270-degree fundoplication is created with three tiers of sutures placed between the esophagus and stomach, and each tier is placed 1.5–2 cm above the other (see Fig. 5). The hiatus is closed posteriorly. A detailed description of the operative technique is reported in a recent publication.[4]

In patients with a peptic stricture, the techniques of esophageal dilatation are essential to achieving optimal results. Most strictures can be dilated before operation, and dilatation up to a size 50 French bougie is desirable. The most severe grades of fibrous stricture may require a more forceful, intraoperative dilatation using Hegar dilators passed in retrograde fashion through a small gastrotomy in the upper gastric fundus. The need for postoperative dilatation is variable and depends on the severity of the stricture. Short, mild strictures are easily

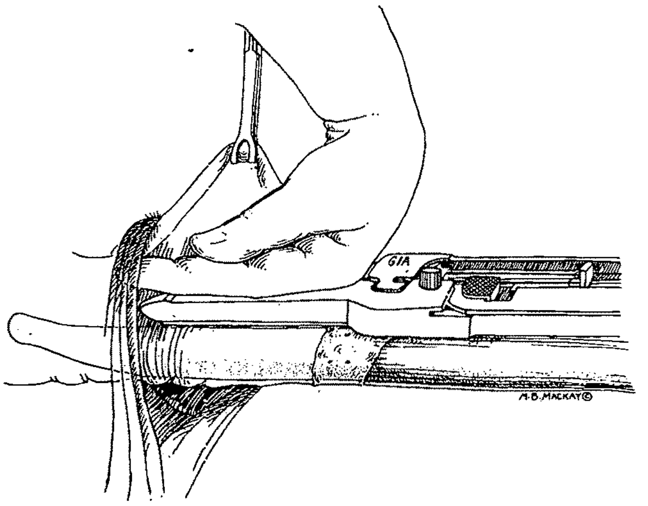

FIG. 3. The stomach is then divided with the GIA stapler, although division between two obtuse angled clamps may be used as an alternative technique. The length of gastric tube created depends on the degree of acquired shortening. A 5-cm gastric tube is sufficient in the majority of cases and can be accomplished with a single application of the stapler. Traction is exerted on the greater curvature side of the fundus before closing the jaws of the stapler. This ensures that the gastric tube closely approximates the diameter of an indwelling No. 48 French bougie throughout its length. The length and diameter of the gastric tube are an important component of the antireflux properties of the repair.

dilated by the single passage of a 50 French Maloney bougie before operation, and rarely require further treatment after repair. Postoperative dilatation will be beneficial in many patients with moderate degrees of stenosis, and in all cases of severe, long stricture. These dilatations are done by indirect bouginage in the out-patient clinic using topical anesthesia that may be supplemented by intravenous diazepam. Intermittent dilatation is continued until the healing process in the esophageal wall is complete and scar contracture has ceased. In the most severe cases, this process of resolution may last for as long as 12–18 months, and during this time, intermittent dilatation may be necessary to maintain normal swallowing.

Follow-up

Follow-up examination was conducted by personal interview on an annual basis during the first 5 years, and at 2-year intervals thereafter. A standard questionnaire was completed at the time of each follow-up examination. Endoscopy, esophageal manometry, and pH studies were not used routinely and were only done in symptomatic patients. Follow-up is complete in 382 patients (90%) and extends from 1 to 20 years. Two hundred fifty patients have been followed up for 5 or more years and 101 patients for more than 10 years.

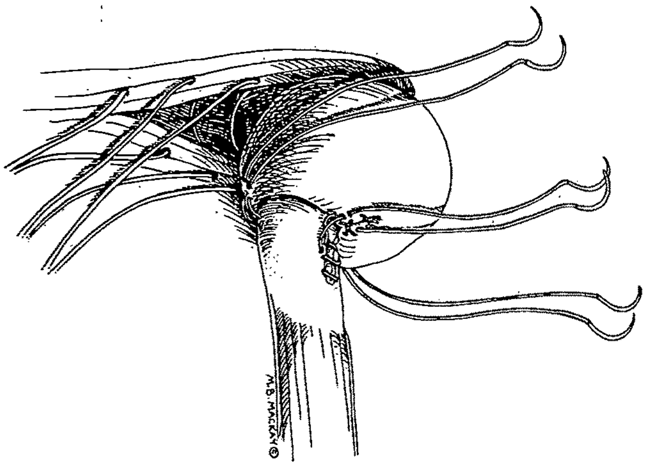

FIG. 4. A partial, Belsey-type fundoplication envelops a 4–5-cm length of the gastroplasty tube. The fundoplication encircles at least 270 degrees of the circumference, and is created with three tiers of double-ended No. 000 silk sutures. The tiers are spaced at 1.5-cm intervals beginning 1.5 cm above the esophagogastric junction and extending proximally. Three sutures are used to secure each tier. In this diagram, the first two tiers have been tied and the third and final tier of three sutures has been placed.

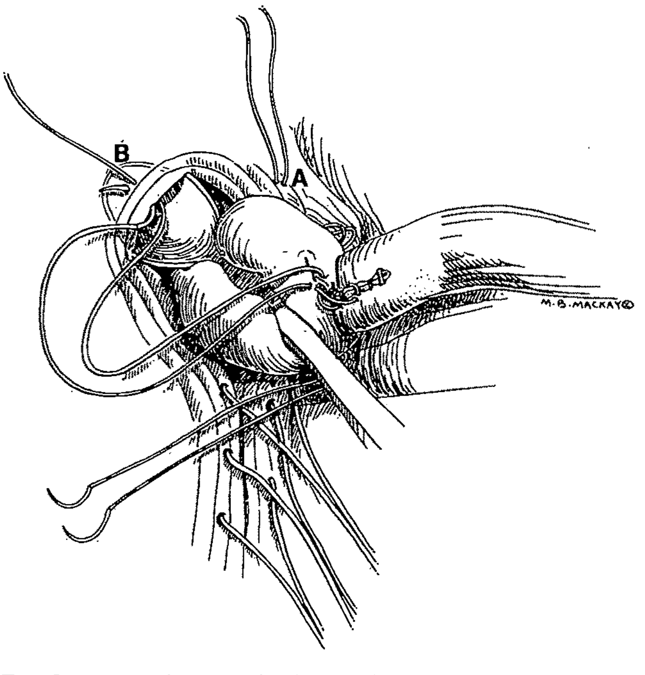

FIG. 5. A spoon is placed in the anterior opening of the hiatus to facilitate passage of the last tier of fundoplicating sutures. These sutures are directed through the hiatus and then brought back up through the diaphragmatic margin from the abdominal to the thoracic side. In this diagram, both ends of the fundoplicating suture on the right side have been passed in this fashion, but not tied, and are situated in the diaphragmatic margin just to the right side of the anterior "apex" of the hiatus (A). The middle suture is in the process of placement just to the left of the "apex" of the hiatus (B). These three sutures are spaced apart in the diaphragmatic margin by the same distances that separate them on the circumference of the gastric tube or esophageal wall.

TABLE 1. *Complications in 424 Patients*

	No. of Patients
Atelectasis, pneumonia	18
Wound infection	12
Esophageal fistula	6
Prolonged incisional pain	17
Other	30

Results

Two patients died within 30 days of operation: one died of a myocardial infarction during operation, and the other died of pneumonia with respiratory failure.

Complications are listed in Table 1. The complications observed in this series are similar in severity and frequency to those anticipated after any of the standard hiatus hernia repairs. There were six esophageal fistulas: none were fatal, and three of the six occurred in patients who had reoperation. Prolonged incisional pain was identified as a significant complaint in 17 patients at more than 1 year after operation.

Functional results were classified as follows: good: asymptomatic, or with inconsequential symptoms requiring no therapy; fair: improved, but with symptoms and/or endoscopic findings requiring intemittent therapy (antireflux medication or dilatation); poor: unimproved or worse. Table 2 is a tabulation of results that have been subdivided into four categories for purposes of this review.

Group 1

There were two hundred fifteen patients with acquired short esophagus due to peptic stricture (138 cases), or severe ulcerative esophagitis without significant stricture (77 cases), who had never had prior antireflux surgery and had no associated primary motor disorder. One hundred twelve patients in this group were followed up for more than 5 years, and 46 of these patients were followed up for more than 10 years. One hundred ninety-eight patients (93%) had good to excellent results sustained over this long follow-up period. Eleven results were categorized as fair because of dysphagia in eight cases, reflux in one case, and both reflux and dysphagia in 1 case. All of the six poor results were due to dysphagia. Two of the six patients with poor results were submitted to further antireflux surgery for the management of persistent ulcerative esophagitis and restenosis. In each case, the partial fundoplication was taken down and then reconstructed using a 360-degree Nissen-type wrap. Two additional patients with good reflux control required reoperation for complications of subsequent duodenal ulcer: one required an antrectomy for pyloric stenosis, and the other required an emergency omental patch for a perforated duodenal ulcer.

TABLE 2. *Results by Category*

	No. of Cases	Results		
		Good	Fair	Poor
Short esophagus due to stricture (138), esophagitis (77) (excluding reoperations and motor disorders)	215	93% (199)	4% (10)	3% (6)
Reoperations: 1 or more previous unsuccessful antireflux operations	118	80% (93)	12% (15)	8% (10)
Peptic stricture (25), or esophagitis (12), associated with a primary motor disorder	37	54% (19)	24% (9)	22% (8)
Intrathoracic stomach	54	91% (40)	9% (5)	0% (0)

Group 2

There were one hundred eighteen patients who had had one or more prior, unsuccessful antireflux operations. There were 149 prior operations in 118 cases. Twenty-two patients had had two or more previous procedures. The types of previous repairs were as follows: transabdominal Nissen fundoplication (65), transthoracic Belsey Mark IV repair (31), transabdominal Hill repair (9), transthoracic Thal operation (3), gastroplasty and fundoplication (1), and unidentifiable repair (9). Follow-up was complete in 101 of 118 patients. Fifty-eight patients were followed up for longer than 5 years, and 23 patients were followed up for more than 10 years. Thirty-eight of 118 patients had a peptic stricture, and an additional eight patients had severe ulcerative esophagitis without significant stenosis.

Good to excellent results were obtained in 93 (80%) of 118 patients. In 15 patients (12%), the result was classified as fair because of both symptomatic reflux and dysphagia in 10 cases, and dysphagia alone in five cases. A poor result observed in 10 patients (8%) was due to reflux and dysphagia in six cases, dysphagia alone in three cases, and reflux alone in one case. Thee of the 10 patients with poor results were reoperated on and all were managed by revision with a complete fundoplication.

Group 3

There were 37 patients with an underlying primary motor disorder: scleroderma (16 cases), achalasia (14 cases), and diffuse spasm (7 cases). All 37 patients in this group had gross endoscopic ulcerative peptic esophagitis, and there was some degree of peptic stricture in 25 of the 37 patients. In patients with achalasia, reflux esophagitis is only seen as a complication that may follow esophagomyotomy. All 14 patients with achalasia had had a previous myotomy, and six of the 14 patients had had an additional antireflux operation in an attempt to control the subsequent complication of reflux. One of 16 patients with scleroderma had had previous antireflux surgery, and one of the seven patients with diffuse spasm had had a long myotomy. Follow-up is complete in 34 of these 37 patients and extends for longer than 5 years in 25 patients, and for more than 10 years in 13 patients.

Long-term results were much less favorable in this group of patients. Furthermore, the quality of result continued to deteriorate with time in a significant number of patients, particularly in cases of achalasia. This trend to continued deterioration was much less apparent in the other groups without an associated motor disorder. The results are tabulated in Table 3. Good results were obtained in only 54% of the 37 patients. The worst results were observed in patients with achalasia, and unmanageable, progressive dysphagia developed in three of these eight patients and they were submitted to thoracic esophagectomy and cervical esophagogastrostomy.

Group 4

There were 54 patients with a massive, sliding hiatal hernia or intrathoracic stomach. It is emphasized that patients with true paraesophageal hernia have a normal esophagus, do not require a gastroplasty, and have been managed by a standard Belsey repair. They are excluded from this group of 54 patients. Thirty-eight of the 54 patients have been followed up between 5 and 10 years, and 11 patients were followed up for more than 10 years. Follow-up is incomplete in five patients. Good to excellent results were obtained in 49 (91%) patients. No patient has required further operation.

Subsequent Adenocarcinoma

An adenocarcinoma that appeared to originate in the distal esophagus was subsequently diagnosed in five patients. All five patients had some degree of acquired columnar-lined esophagus, and four of the five had associated peptic strictures. A diagnosis of carcinoma was established between 3 months and 7 years after gastroplasty and fundoplication. In two patients, the adenocarcinoma was diagnosed at 3 months and 9 months after repair, and may well have been present as an occult tumor at the time of repair. In the remaining three patients, the tumor was identified after 2.5, 3, and 7 years and was probably not present at the time of the repair. Only one of these three patients was known to have poor reflux control after gastroplasty and fundoplication, a patient with scleroderma and a peptic stricture whose cancer was identified 7 years after antireflux surgery.

TABLE 3. *Primary Motor Disorders*

	No. of Cases	Results		
		Good	Fair	Poor
Scleroderma	16	9 (57%)	4	3
Achalasia	14	6 (43%)	4	4
Diffuse spasm	7	5 (71%)	1	1

Discussion

Throughout the study we have used gastroplasty and fundoplication in all patients with dilatable peptic strictures selected for operation. During this same period, we have operated on 15 patients with undilatable strictures, and these patients were managed by distal esophagectomy and short colon interposition. In an additional patient, instrumental perforation of a severe stricture was managed by a Thal esophagogastroplasty. Various authors continue to recommend differing options for the management of patients with peptic esophagitis, stricture, and acquired short esophagus. Preferences range from a standard repair (Nissen, Belsey, Hill) to resection and replacement. Among the standard repairs, Hill's procedure is the only one that reports a high proportion of good results obtained in large numbers of patients with long-term follow-up.[5,6] Intrathoracic antireflux reconstructions such as the Thal procedure[7] or the intrathoracic Nissen fundoplication[8,9] may provide good reflux control with resolution of esophagitis and stenosis. The quality of result after intrathoracic reconstructions may be impaired, however, by an unexpectedly high incidence of gastric ulceration in the intrathoracic stomach or progressive, massive herniation on long-term follow-up. The addition of gastroplasty to an antireflux repair assures a tension-free reconstruction and an anatomic recurrence of the hernia is rare after this operation. In our series of patients with acquired short esophagus due to esophagitis and dilatable peptic stricture, good results were obtained in more than 90% of patients who did not have an underlying primary motor disorder or a history of previous antireflux surgery. This high proportion of good results was sustained over long periods of follow-up and was achieved with a low operative mortality and a morbidity that was no greater than that anticipated after any standard hiatal repair. We again emphasize the important need for postoperative dilatation in patients with severe strictures that may undergo a very slow resolution of the inflammatory changes responsible for continuing scar formation and contracture after good reflux control has been achieved.

Reoperation after unsuccessful previous antireflux surgery yields significantly fewer good results. There are relatively few publications to date that report the results of reoperation in large numbers of patients with failed, antireflux surgery.[10-15] It is apparent from these reports that these reoperations are often technically difficult, and expertise with the operative management is only achieved after significant experience. The optimal procedure in any given patient can be unpredictable and may be determined only at the time of exploration and mobilization. Preoperative preparation should include consideration of a resection, which is necessary in some cases and may only be determined at the time of surgery.[14,15] The potential for good results diminishes with the number of reoperations. Little et al.[14] advise serious consideration of resection in patients who have had more than two previous repairs. The results of gastroplasty and fundoplication in patients who were reoperated on have been reported by Henderson and Marryatt[13] and Orringer.[15] These authors favor a complete Nissen-type fundoplication, and both reports indicate that the results of reoperation for reflux problems are less satisfactory. In our own series, the number of unsatisfactory results (20%) was more than double that observed in patients with acquired short esophagus and stricture undergoing a first operation (7%). Nevertheless, 80% of these patients had good results that were sustained through long follow-up periods, and this was achieved without any operative mortality and an acceptably low morbidity in 118 cases.

By far the most difficult group of patients are those with ulcerative reflux esophagitis and peptic strictures that are associated with an underlying primary motor disorder. Among these motor disorders, achalasia presents the most difficult problems in management. When ulcerative reflux esophagitis and stenosis develops after esophagomyotomy for achalasia, there appears to be no conservative operation that will control both reflux and dysphagia in these patients with an aperistaltic esophagus and absent distal sphincter. Good results were obtained in only six of our 14 patients with achalasia, and three of the four patients with poor results have ultimately required resection and replacement of the thoracic esophagus. As a result of this experience, we currently recommend serious consideration of resection in any patient with achalasia who has endoscopic confirmation of gross ulcerative peptic exophagitis or peptic stricture. Gastroplasty and fundoplication may still be the best option for patients with intractable reflux symptoms in the absence of ulcerative esophagitis or stricture. We continue to recommend this conservative operation in patients with esophagitis and stricture associated with scleroderma. Of 16 patients with scleroderma, 13 have had sustained improvement (9 good, 4 fair) in our series. Our experience with cases of diffuse spasm associated with significant reflux esophagitis is too small to warrant further comment.

In conclusion, gastroplasty and fundoplication provides a high proportion of good results in patients with acquired, short esophagus due to peptic esophagitis. The addition of gastroplasty assures a tension-free repair in patients with obvious acquired shortening and is also recommended in cases of reoperation for failed antireflux surgery and for massive sliding hernias since subtle degrees of shortening are commonly encountered. The presence of a primary motor disorder in association with peptic esophagitis and stricture has a severely adverse effect on results, which continue to deteriorate throughout long follow-up periods. The poorest results occur in patients with achalasia, and in such patients, serious consideration should be given to esophageal resection rather than a more conservative repair.

Acknowledgments

We thank Mrs. N. Blair and Mrs. J. Basiuk for their help in organizing and conducting the long-term follow-up of these patients.

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DISCUSSION

DR. DAVID B. SKINNER (Chicago, Illinois): I greatly enjoyed both of these papers that raised several important issues.

In regard to Dr. Bombeck's paper, he has introduced a sophisticated new method for manometry that raises the possibility as to the application of this for the selection of patients for antireflux surgery. To put this into perspective, manometry was first proposed for this purpose over 30 years ago by Code et al. and about 20 years ago it was found not to be very effective in selecting patients with an incompetent cardia based on the technology at that time. Therefore, pH testing was introduced with the standard acid reflux test, and then a little over 10 years ago the 24-hour pH study was introduced as the gold standard for assessing this problem.

Dr. Bombeck is suggesting that going back to pressure measurements rather than direct measurements of reflux by pH testing may be applied to the selection of patients for surgery. I believe considerably more experience will have to be obtained with this new technique before we can say whether his thesis can be supported or not, but I do believe it is an important technological breakthrough in our ability to evaluate and study the distal esophageal sphincter mechanism. As a research tool, this should prove highly valuable in understanding some of the complex mechanisms that go into the normal control of gastroesophageal reflux.

I have a few specific questions for Dr. Bombeck. On his slide where he compared the pressure in the area with the LESVV, he had considerable fewer points on the LESVV bar than he did on the other ones, and I wondered how he selected those cases that showed such a nice clear discrepancy on that far right-hand bar compared with the other charts that he showed.

He also told us that he knew the LESVV before starting patients on therapy and then told us that those with the lowest LESVV were selected for subsequent surgery, but he did not tell us why they were selected for surgery.

Is this a self-fulfilling prophecy since he knew ahead of time what the values were in his study? I believe we are still selecting patients for antireflux surgery based on documentation of reflux (pH testing remains the standard for that) and based on the complications of reflux. I do not believe we should be selecting patients for surgery based simply on a manometric measurement since the disease is not a hypoactive LESVV but is reflux esophagitis, which can be assessed more directly by pH testing and by endoscopy. However, I do believe we have heard a very elegant new technique that would be of interest in the future as we refine our knowledge of this.

Dr. Pearson, of course, is the world leader in the evaluation of the gastroplasty operation. We have all admired his experience for many years. I disagree with him about some of the indications that he has used it for. We have had this disagreement over many years, and I will not repeat it here.

I do have two specific questions for him, however. The incidence of five cases of adenocarcinoma in this disease brings to mind the incidence of cancer in Barrett's esophagus, and in fact, the gastroplasty is an iatrogenic form of Barrett's esophagus. If I did my math correctly, his incidence of cancer is approximately 1 in 450 to 1 in 500 patient years of follow-up, which is not significantly different from the 1 in 400 patient years of follow-up incidence of cancer that Cameron reported in Barrett's esophagus cases from the Mayo Clinic. This does raise one question: is this gastroplasty operation a form of Barrett's esophagus biologically as well as technically? I would like to ask him in the patients that he has endoscoped in follow-up, has there been metaplastic epithelium, the type that we see in Barrett's as a harbinger of the potential malignant degeneration?

Second, when he does the gastroplasty he leaves a 5 cm or more segment of nonperistalsing tubular digestive swallowing tube, and I wonder what proportion of his patients continue to have some degree of dysphagia because of the interposition of a nonperistalsing tube below their esophagus.

DR. MARTIN ALLGÖWER (Basel, Switzerland): Ever since my secretary fell in love with Dr. Bombeck I knew that he was up for very sophisticated techniques (Laughter).

Now, if I am getting up as a discussant for the third time today, I apologize, but being the successor of Professor Nissen, I believe this gives a certain legitimisation, and Dr. Bombeck kindly asked me to comment on his paper.

It is obvious that my former chief invented the right operation for probably the wrong reason (but that is a much better thing than the other way around!).

I believe one fact that we could contribute in recent years and with which Dr. Bombeck agrees is the work of Dr. Liebermann. She could prove that there is an anatomic corollary to the lower esophageal sphincter, a fact contested by certain anatomists. Dr. Liebermann, working on cats, correlated her morphologic findings to the function of the LES, evaluated in these animals by pullback manometry. In light of these facts, Dr. Bombeck's findings are a most important adjunct to our diagnostic armamentarium in the patient.

Two questions to Dr. Bombeck: I wonder how much his CAM will replace what we formerly got in information from radiology, endoscopy, and pH monitoring. Furthermore, in a recent meeting in Switzerland there was some agreement that beyond all objective data, the amount of suffering may influence indications although you cannot really get data on this element.

My second question: what about other pathophysiologic mechanisms that have been accused of being instrumental: the length of the abdominal segment and the gastric secretion? Is this now all out?

DR. TOM R. DEMEESTER (Omaha, Nebraska): I am appreciative to both Drs. Bombeck and Pearson for having the opportunity to review their manuscript. The definition of gastroesophageal reflux disease is not precise. Some define it as the presence of the symptoms of heartburn and regurgitation. This definition is too selective that many patients with the disease are dismissed as not having the disease because their symptoms do not conform to the definition. Some define the disease as the presence of esophagitis, but esophagitis is a complication of reflux, which only 40–50% of the patients manifest. We would define the disease on the basis of what it is, an increased esophageal exposure to gastric juice. This can be measured objectively by 24-hour esophageal pH monitoring. The problem becomes more complex in that there are a number of causes for increased esophageal acid exposure. This is where Dr. Bombeck's work comes into perspective because his use of computer technology has allowed him to identify when a mechanically defective cardia is the cause for increased esophageal exposure to gastric juice; a subject in which we have a great deal of interest. He has integrated sphincter pressure and length together into a single measurement for determining competency of the cardia.

One aspect of the sphincter that his approach does not measure was pointed out by Dr. Allgower, that is, the position of the sphincter and whether it is exposed to abdominal or thoracic pressure. I would ask Dr. Bombeck if he believes the position of the sphincter is important and how would he integrate this into his measurement.

The fact that he was able to separate patients into those with a good and bad sphincter early in the course of the disease might be an indication for early operation instead of waiting until complications of the disease occur. Could he tell us how his measurement compares with standard motility measurements for pressure and length. Are patients with abnormal values on standard motility for pressure, overall length, and abdominal length likely to be abnormal on his computer analysis? If so, then do we need such a sophisticated computer technique to make this differential? I suspect that the computer analysis program described by Dr. Bombeck will be shown to be superior to standard motility and represents a step in the development of diagnostic criteria based on recording and analysing large amounts of data using the office computer.

I shift my comments to Dr. Pearson's presentation. I congratulate him on his 93% success rate for uncomplicated patients with gastroesophageal reflux. We found exactly the same success rate based on a 10-year follow-up evaluation of 100 consecutive abdominal Nissen fundoplications done for uncomplicated reflux disease. Consequently I do not appreciate the need for the addition of a gastroplasty, particularly when in Dr. Pearon's experience it led to six fistulas.

Motility studies in patients with a gastroplasty tube have shown that the tubes are adynamic. It appears that this adynamic tube causes no difficulty in esophageal clearance who have good esophageal contractions, but as soon as that esophagus contractility deteriorates, as in the presence of a motility disorder, the adynamic tube may function as a retard to esophageal clearance. Dr. Pearson, have you seen these problems?

I am also concerned about the passage of medication through these gastric tubes. Do oral tablets clear or are they prone to become trapped in the tube and cause mucosal injury? Are the patients instructed on any specific precautions regarding taking the medication after they had a gastroplasty?

Lastly, I am concerned about the incidence of cancer in these patients. If the gastric tube secretes acid, which fails to clear adequately, then a Barrett's esophagus may develop due to the constant acid environment. The use of the gastroplasty may set up the potential for malignancy. This is a very important factor. The incidence of malignancy in 100,000 patients with Barrett's esophagus is about 500 at the lowest estimate. That is almost 1.5 times the incidence of lung cancer in 100,000 patients who smoke.

DR. JOHN R. BENFIELD (Los Angeles, California): We are indebted to Dr. Pearson and the Toronto group for the long-term follow-up regarding their use of the Collis gastroplasty. The routine use of gastroplasty has been associated with more than 90% good results in patients operated on for the first time. This fact in itself represents a significant improvement as compared with the more usual reports of about 85% good results from first time treatment of reflux esophagitis.

The main potential disadvantage of gastroplasty, other than that pointed out by Dr. Skinner and Dr. DeMeester, is the risk of fistula. Since this complication occurred in less than 2% of the patients who had gastroplasty without death as a result of the use of this approach, Dr. Pearson's argument becomes significantly convincing.

Having had the occasion to work with Dr. Pearson in Toronto during the early days of their use of gastroplasty, I became convinced that the meticulous removal of the fat pad at the cardioesophageal function is, indeed, a main feature in making this operation a success, and I would like to stress that.

With Dr. Pearson I have had the frustrating problems of achalasia in association with reflux esophagitis and hiatus hernia, culminating in the need for cervical esophagogastrostomy.

I agree that the combination of a primary motor disorder with esophagitis is a difficult problem, fortunately rare in my experience, and perhaps is best managed with primary resection.

I am frankly a bit bored with the discussion as to the relative merits of total fundoplication as compared with the Belsey approach in the treatment of reflux esophagitis. Nevertheless, the fact that the Toronto group treats failures from dysphagia after Belsey procedures with the use of complete fundoplication is noteworthy. Indeed, one of the main causes for failure of Nissen procedures is dysphagia.

Dr. Pearson, since you rely on complete fundoplication for the management of treatment failure, why do you not use the Nissen procedure for the initial form of fundoplication?

DR. C. THOMAS BOMBECK (Closing discussion): I would especially like to thank Drs. Skinner and DeMeester for their comments. I am not sure whether I want to thank Professor Allgower or not.

Dr. Skinner is quite correct. This is a new method. This is a refinement of an old method that has been made possible by the addition of the microcomputer and the high-speed A to D interface, and we could not have done this before.

A great deal more experience is needed with it before we can actually say what it is going to be good for. It certainly does have a good theoretical background in that it is supported by just simple standard high school physics as to why it works, and indeed, in the initial test it does seem to work.

He asked why do this, why not use standard pH testing and so on because those demonstrate reflux adequately. Indeed they do, and the benefit of this particular method is not that it demonstrates the patients who will reflux, that separates the refluxer from the nonrefluxer, because pH testing does that better. What it does do, however, is look at why the patient is refluxing and measure the competence and the residual competence of the lower esophageal sphincter. It will pick out the patients who have enough residual competence that they can benefit from medical therapy *versus* the patients who do not.

You asked about the separation between patients who eventually came to operation and those who did not. Those were patients who were studied before they began medical treatment. They went through a course of 6 weeks of medical treatment. Some flunked it, and they had operations. Others had their reflux esophagitis greatly improved, and they were continued for another six weeks, and if they did, they were withdrawn.

Those who failed the treatment were the ones who eventually had operation and those who did not were the ones who were counted as medical successes, and this method clearly distinguished those patients.

You asked about the discrepancy between the number of patients on that one slide, and I do apologize for that. That was early in the series. The slide that shows the separation much better is the last one, which shows the nonrefluxers at the top, the medical successes in the middle, and the Nissens at the bottom, and that includes the whole series that shows the same degree of refluxers and nonrefluxers.

Both Dr. DeMeester and Professor Allgower asked about the length of the abdominal segment and where does this come in. The length of the abdominal segment is a relative thing. All lower esophageal sphincter lengths are relative things. These are not actual anatomic lengths. These are simply the length over which one measures an increased pressure, and what it has to do with the actual length of the sphincter is not clear. For that reason, if the sphincter is moved into the thorax, the relative length may actually go down simply because of negative intrathoracic pressure.

Regarding length of the abdominal segment, we do not believe that that is terribly important simply because of the mechanism by which the Nissen works. Whether it is important in the patient who refluxes or not is very difficult to say because this moves all the time.

What about gastric secretion? Gastric secretion has no role in worrying about gastroesophageal reflux except that one has to have some acid if one is going to have acid esophagitis, but it is not a disease of gastric hypersection and should not be treated that way.

Finally, Dr. DeMeester asked about what is new about this. We have had very low, lower esophageal sphincter pressures. The patient who has a very low lower esophageal pressure is going to have a very low or nonexistent LESVV as well. The patients we are concerned about are those who are somewhat higher. We are concerned about that large amorphous group of patients between medical failures, true medical failures, and medical successes. That group right in the middle that we cannot predict, that we do not know what is happening to them because we have no way of fully quantifying their LES, this will do that. We do not need it for the patient whose LES pressure is zero.

DR. F. G. PEARSON (Closing discussion): I would like to thank my colleagues for their comments and questions.

There were several questions. Dr. Skinner and Dr. DeMeester raised the issue of adenoma developing in these patients, and it is certainly a serious concern. The majority of the patients in the series have the latest, the most advanced stages of peptic esophagitis, and my judgment would be that well over 200 patients in this series have some degree of acquired columnar line esophagus. Many of these patients were operated on in the 1960s in the days before we were documenting that clearly, and the first three cancers occurred during that time.

I can only say, Dr. Skinner, that my assumption has been that these are cases of carcinoma that are developing in the columnar line segment, and two of them developed within 3 months and 9 months of operation. I believe they were almost certainly there when we did the initial surgery.

The last case that we have encountered is the patient seen at 7 years. This patient had scleroderma, inadequately controlled after operation as far as reflux was concerned, and he had a definite, long columnar line segment. In that patient, cancer in the columnar line segment, not in the gastric tube, developed 7 years later. I had not even considered that prospect until you raised the question.

The gastric tube both Dr. Skinner and Dr. DeMeester have noted would appear to be an inert tube. Is it related to dysphagia? As long as the tube is not created at too small a diameter, and that is why we leave in that bougie when it is constructed, I do not believe it is ever responsible for dysphagia by itself. It is, in fact, functional and not inert, and we did many intraoperative studies using a system with a terminal transducer, and clearly identified that that gastric tube functions similar to the distal esophageal sphincter in two areas. First, it does relax in response to swallowing, and it will respond to drugs such as atropine, and will drop the pressure. Gastrin will elevate the pressure, and a colleague of Dr. Allgower's in Switzerland, Dr. Leibermann, has done some elegant anatomic studies on the anatomic disposition and function of this lesser curvature part of the stomach from which the tube is created. I believe there is good evidence from that study and other studies that lesser curvature is almost a part of the lower esophageal sphincter mechanism. Therefore, it is certainly not an inert tube.

Dr. DeMeester, I remind you that when I have used the word "uncomplicated cases," I mean uncomplicated by reoperation or a motor disorder. These still represent a group of patients with the most advanced degrees of esophagitis, and I do not believe that a sequential group of Nissen fundoplications will result in a consecutive series of long-term results of this quality, if you wish, because some of those patients simply have too short an esophagus for any of the standard repairs other than possibly a Hill repair to be effective.

Dr. Benfield emphasized the importance of technique, and I would think one of the disadvantages of this operation, and it is a significant one, is that it is technically difficult. It is not an easy operation to pass on to the resident. The Belsey operation is in the same category, but this is even more so.

Dr. Benfield, you also asked about using a complete fundoplication for the reoperations. We did not use it right off the bat because we were reoperating for patients with dysphagia. The dysphagia in our failures is due to recurrent stenosis and stricture, which is due to a failure to control reflux. I do not have any doubt that a complete fundoplication provides better reflux control. Our concern has been that used routinely with this particular reconstruction we would have a higher incidence of mechanical dysphagia using a complete fundoplication than the partial operation.

Prolongation of Pig-to-Dog Renal Xenograft Survival by Modification of the Inflammatory Mediator Response

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The pathogenesis of hyperacute renal rejection consists of a nonspecific effector cascade that invokes most of the components of a typical acute inflammatory response. Platelet-activating factor (PAF) represents the most recent and perhaps the most significant mediator and promoting agent of this phenomenon. These studies evaluated SRI 63-441, a novel, synthetic, and the most potent PAF receptor antagonist available, alone and in combination with other prostanoids, for their ability to influence this response and to prolong renal xenograft survival and function in a model of pig-to-dog heterotransplantation. Inhibition of PAF by SRI 63-441 alone, at the dosage and schedule used in these experiments, did not significantly prolong xenograft survival or function. However, the combination of SRI 63-441 with either prostacyclin (PGI_2) or prostaglandin E_1 (PGE_1) infusion demonstrated significant synergism, and resulted in a 6–9-fold increase in kidney survival and a 3–20-fold increase in urine output. Neither PGI_2 nor PGE_1 infusions alone significantly influenced this xenograft model. Electromagnetic flow studies demonstrated significantly delayed diminution in renal artery blood flow in the combination-treated animals. Serial and end-stage histologic examination of kidneys receiving combination therapy demonstrated a delayed onset of the pathologic deterioration and an overall amelioration of the entire process. These studies demonstrate that significant abrogation of a rapid and violent form of hyperacute rejection can be achieved solely by the pharmacologic manipulation of the inflammatory mediator response.

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THE PATHOPHYSIOLOGIC EVENTS leading to hyperacute allograft rejection have been relatively well characterized and differ little today from the process originally described almost 20 years ago.[1-3] The initiating event is clearly a specific immunologic reaction consisting of antibody-mediated injury directed against antigens on the vascular endothelium of the transplanted organ.[4-6] This immunologic phenomenon leads to the accumulation of platelet-polymorphonuclear leukocyte-erythrocyte plugs in small arteries and capillaries, followed by intravascular coagulation and ischemic necrosis.[1,4,5,7]

The sequence of events leading from the initial specific immunologic reaction to the final characteristic pathologic result of hyperacute rejection of a kidney, which can best be described as a failure or breakdown of the microvasculature, represents a nonspecific, intense, and complex inflammatory response. This effector cascade invokes most, if not all, of the classical mediator systems of the acute inflammatory process (*i.e.*, complement, coagulation, fibrinolytic, and kallikrein-kinin systems).[8,9] During this process, a large number of biologically active molecules are generated that are responsible for the increased vascular permeability, arteriolar vasoconstriction, damage to the cytoskeleton, fibrin deposition, generation of oxygen-free radicals, and the recruitment, activation, and release of various inflammatory cells, which all contribute to the entire pathogenesis of hyperacute kidney rejection.[8,9]

Many of these chemical mediators of inflammation, including kinins, various chemotactic factors, anaphylatoxins, serotonin, and arachidonic acid metabolites

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(prostaglandins, leukotrienes, thromboxanes) have been proposed as central candidates in the overall process of hyperacute rejection, and have served as the targets in attempts to develop therapeutic interventions to regulate organ function. The newest and perhaps most important inflammatory mediator to be nominated as a central candidate in the overall evolution of hyperacute rejection is acetyl glyceryl ether phosphorylcholine (AGEPC).[10] Also known as platelet-activating factor (PAF), as it will be referred to here, because it was initially discovered by its ability to cause potent platelet aggregation and release, it represents the most recently described and novel class of potent lipid autocoids.[8,11,12]

The implication that PAF plays a central role in the induction of tissue injury is attributed to a spectrum of biological activities that may manifest all of the cardinal signs of acute inflammation.[8,10-12] PAF is produced by a variety of inflammatory cells including platelets and neutrophils. It is also produced by endothelial cells, which supports its importance as a key regulator of the microvasculature, and more importantly, its disruption under pathophysiologic circumstances. Specific biological activities of PAF that are germane to its role in hyperacute rejection include: platelet and neutrophil release and aggregation, release of thromboxane A_2 and other eicosanoids, increase of vascular permeability, vasoconstriction, increase in hematocrit, systemic hypotension, and generation of oxygen-free radicals.

With the availability of specific receptor antagonists of PAF, further insight into the role of PAF in the pathogenesis of hyperacute rejection is now possible. The potential for a new method of controlling the effector cascade of hyperacute rejection by pharmacologic intervention can now be exploited also. Pig-to-dog renal heterotransplantation results in a rapid and violent form of cortical necrosis and ischemic destruction of the organ, which mimics the situation in humans and is due to preformed humoral antibodies in the recipient.[4,5,13] It represents an appropriate severe model in which to evaluate new methods of therapeutic intervention. The studies reported evaluated the effect of a novel and potent synthetic PAF receptor antagonist, alone and in combination with other prostanoids, on this renal xenograft model.

Materials and Methods

Animals

Female, white outbred SPF pigs that weighed 15–20 kg were purchased from Shadyside Farms, Ohio and served as donors. Male beagles that were bred for research and weighed 13–16 kg were purchased from Laboratory Research Enterprise, Kalamazoo, Michigan and served as recipients. All animals were housed in a central animal facility and were allowed to acclimatize for at least 1 week before experimentation. They received standard animal chow and water *ad libitum* and were fasted for 24 hours before surgery.

Surgical Procedures

All animals for both the donor and recipient procedures were anesthetized with intravenous sodium pentobarbital (30 mg/kg). Recipient dogs were maintained with 30% oxygen through an endotracheal tube. During the experimental procedure, dogs were monitored for depth of anesthesia by EKG and arterial pressure. Additional anesthetic (pentobarbital, 3 mg/kg IV) was given as required.

Donor pigs received intravenous Ringer's lactate (1000 mL), mannitol (12.5 g), and Thorazine® (50 mg). After systemic heparinization (5000 units) and *in situ* cooling with cold (4 C) Ringer's lactate through an aortic cannula, the kidneys were removed *en bloc.* The kidneys were then separated and transplanted simultaneously into two recipient dogs, always with less than 1 hour of cold ischemia time. A paired design was therefore performed for each experiment, by assigning one kidney as the control and the other as the test (treated) kidney.

All pig-to-dog kidney heterotransplantations were performed by a standard technique. The porcine renal artery was anastomosed end to end to the recipient right common iliac artery, and the renal vein was anastomosed end to side to the right common iliac vein. The anastomosis time was always less than 30 minutes. The dogs were kept anesthetized and the kidney was left external to the dog for observation. The ureter was cannulated with polyethylene tubing and urine was collected throughout the transplant period. For intra-arterial administration of prostaglandins, an 18-gauge polyethylene catheter was inserted through the middle sacral artery and threaded towards the orifice of the right common iliac artery. To ensure that solution infused into the terminal aorta would exclusively run into the graft renal artery, the left common iliac, middle sacral, and other smaller arteries originating at or near the aortic bifurcation were ligated near their origin. For those experiments where renal vein and artery platelet counts were measured, 18-gauge polyethylene catheters were introduced into the right femoral vein and its tip positioned at the venous anastomosis, and into the left common iliac artery and its tip positioned at the orifice of the right common iliac artery.

Each dog underwent native nephrectomy after the porcine kidney had been revascularized. A change in color or motling of the transplanted pig kidney was considered evidence of the onset of rejection. However, the end point of the experiment was signaled by a cessation of urine flow or by the onset of frank hematuria.

Drug Administration

Prostaglandins. Naturally occurring prostacyclin (PGI_2) and prostaglandin E_1 (PGE_1) or Prostin-VR were supplied by the Upjohn Company, Kalamazoo, Michigan (M. J. Ruwart). PGI_2 was reconstituted and infused in a 0.1M glycine buffer, adjusted to a pH of 10.5 with 2M Tris solution to enhance its stability. PGE_1 was reconstituted in a stock solution of 1 mg in 100 μL of ethanol. This solution was then diluted to the appropriate concentration in 0.9% sodium chloride for infusion.

All prostaglandins, freshly reconstituted for each experiment, were administered by constant infusion through the catheters placed into the aorta, and the dosage was titrated according to blood pressure tolerance. Control animals for the prostaglandin experiments received infusions of the particular prostaglandin vehicles.

PAF antagonist. SRI 63-441 was provided by the Sandoz Research Institute, Sandoz, Inc. (East Hanover, NJ). This synthetic compound represents the most potent receptor antagonist of PAF responses known to date. SRI 63-441 (molecular weight 662) is a substituted [tetrahydrofuranyl-(methoxyphosphinyloxy)ethyl] quinolinium compound[14] and is structurally similar to PAF. Structural analyses and purity (greater than 98%) were determined by NMR spectroscopy and thin-layer chromatography.[14] SRI 63-441 is readily soluble in water or sodium acetate buffer at concentrations as high as 5% and can only be given parenterally. In four species tested (rats, guinea pigs, dogs, and primates), SRI 63-441 exhibited dose-dependent inhibition of all major physiologic responses to PAF (*i.e.*, hypotension, hemoconcentration, bronchoconstriction, and increased vascular permeability).[14] For all studies reported here SRI 63-441 was reconstituted as a 10 mg/mL solution in 0.68% sodium acetate and 0.9% sodium chloride (pH 5.3). Before its administration, this solution was placed in a warm water bath (24–25 C) for 5 minutes and then administered as a bolus intravenous injection. Control dogs received the sodium acetate buffer intravenously.

Experimental Design

Four experimental groups are reported: Group I: the administration of SRI 63-441 alone was compared with controls; Group II: the combination of SRI 63-441 and PGI_2 was compared with controls; Group III: the combination of SRI 63-441 and PGE_1 was compared with controls; Group IV: the combination of SRI 63-441 and PGE_1 was compared with PGE_1 alone.

Both prostaglandins (PGI_2, PGE_1) were administered at a dose of 0.5–1.0 μg/kg/min (depending on systemic blood pressure) by continuous intra-arterial infusion commencing at 30 minutes before revascularization. SRI 63-441 was administered at 5 mg/kg/dose by intravenous bolus beginning at 5 minutes before and then 5 minutes after, and then every 15 minutes after revascularization. For each study, experiments were performed on control and test animals simultaneously.

Kidney survival was assessed for each experiment as described above. Urine was collected for the entire transplant period, and the total volume was used as an indicator of renal function. For six experiments in Group II and for three experiments in Group IV, platelet counts in the renal artery, renal vein, and peripherally were determined serially (every 10 minutes for the first hour and then every 30 minutes for up to 4 hours in the treated groups). Renal arterial blood flow in the transplanted kidneys was monitored electromagnetically using a Cliniflow II, Model FM701D Electromagnetic Flowmeter (Carolina Medical Electronics Inc., NC). Flows (in milliliters per minute) were determined every 10–15 minutes in six separate experiments in Group IV (controls received PGE_1 infusion). Serial kidney biopsies (every 15 minutes) were performed in an extra group of animals that are not included in survival statistics. Biopsies were also done at the end point of the experiment, (using the criteria outlined above) in all groups studied.

Pathologic Studies

Tissue preparation. Histologic evaluation of serial biopsies from one experiment and of sections of kidneys taken at the end stage of additional experiments are presented. In the serial studies, wedge biopsies were obtained at baseline (back table), and at 5, 15, 30, 45, 60, 75, and 90 minutes after revascularization. Tissues were formalin-fixed, paraffin-embedded, cut at 3 μm, and stained with hematoxylin and eosin.

Histologic parameters. One microscopic section from each biopsy was selected. The slides were randomized and evaluated in blind fashion. The percentage of glomeruli with segmental or global thrombosis was determined. The glomeruli with necrosis or PMNs were also counted. Acute tubular necrosis (ATN), characterized by disintegration and sloughing of epithelial cells, was graded as mild (rare foci), moderate (numerous foci), or severe (confluent). Blood in the tubular lumens and mitoses were noted. The interstitium was rated as normal, congested, or hemorrhagic; the latter was graded as mild (few foci), moderate (numerous foci), or severe (confluent). Arteries and arterioles containing thrombi were noted.

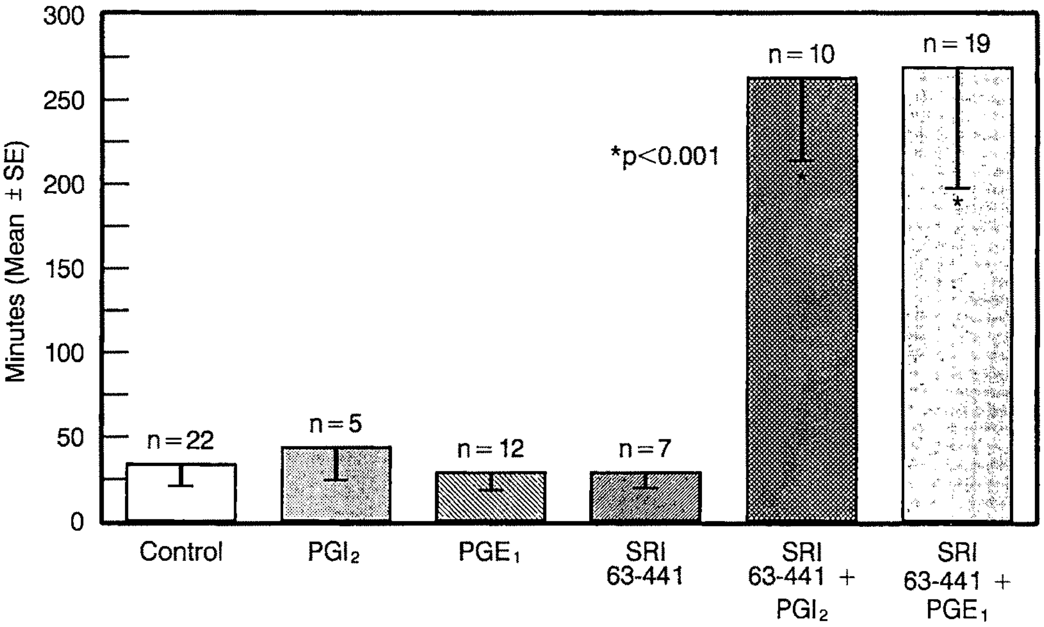


FIG. 1. Survival of renal xenografts after pig-to-dog kidney transplantation assessing the effect of single and combination treatment with a PAF receptor antagonist (SRI 63-441) and two prostanoids (PGI_2 and PGE_1). Results are expressed as total survival time (mean minutes ± SE).

Statistical Evaluation

All statistical evaluations were performed on an IBM PC-AT microcomputer using statistical analysis software (SPSS/PC+, SPSS Inc., Chicago, IL and BMDP/PC, BMDP Statistical Software, Los Angeles, CA). The mean and standard errors for urine volume and kidney survival for control and treated groups were compared using a nonparametric statistical test (McNemar) for the comparison of mean differences between two groups. The mean and standard errors for platelet counts were compared using a repeated measure design analysis. For all tests, a p value of less than 0.05 was considered statistically significant.

Results

Renal Xenograft Survival

Figure 1 depicts the survival for transplanted porcine kidneys in the four groups studied. The control dogs in all experiments consistently demonstrated violent rejection of the pig kidney within a mean time of approximately 30 minutes. The administration of SRI 63-441 as a single agent at the dosage and schedule described here did not result in a significant increase in graft survival. The addition of either prostanoid (PGI_2 or PGE_1) to SRI 63-441 treatment resulted in a marked synergism and a significant increase in kidney survival. SRI 63-441 and PGI_2 resulted in a greater than sixfold (217.1 ± 39.4 *vs.* 37.4 ± 11.1 minutes, $p < 0.001$) and SRI 63-441 and PGE_1 in a greater than sevenfold (268.6 ± 27.7 *vs.* 37.2 ± 5.6 minutes, $p < 0.001$) increase in renal xenograft survival when compared with their respective controls. PGI_2 or PGE_1 infused as single agents had no significant effect on kidney survival. In fact, in Group IV, the combination of SRI 63-441 and PGE_1 resulted in a greater than ninefold increase in kidney survival when compared with PGE_1 infusion alone (280.4 ± 31.8 *vs.* 31.0 ± 11.1 minutes, $p < 0.001$). PGE_1 in this experiment behaved no differently than the control vehicles in the other experiments.

Renal Xenograft Function

Renal function as determined by total urine output for each transplant is depicted in Figure 2. The results parallel those observed for kidney survival already presented above. SRI 63-441 alone did not significantly improve renal function. The combination of SRI 63-441 and PGI_2 resulted in a greater than threefold (99.5 ± 30.4 *vs.* 29.5 ± 13.7 mL, $p < 0.05$) and of SRI 63-441 and PGE_1 in a greater than 20-fold (436.2 ± 134.8 *vs.* 21.2 ± 7.3 mL, $p < 0.02$) increase in total urine output. Neither prostanoid alone resulted in a significant increase in urine output. The combination of SRI 63-441 and PGE_1 resulted in a 12-fold increase in total urine output (370.9 ± 78.9 *vs.* 32.7 ± 6.4 mL, $p < 0.003$) when compared with PGE_1 alone, which did not differ significantly from vehicle controls.

Platelet and Flow Studies

The serial platelet counts for six experiments in Group II (SRI 63-441 + PGI_2 *vs.* controls) and three experiments in Group IV (SRI 63-441 + PGE_1 *vs.* PGE_1) are depicted in Figures 3 and 4, respectively. There was a significant difference between the renal artery and renal vein platelet counts in Group II for both

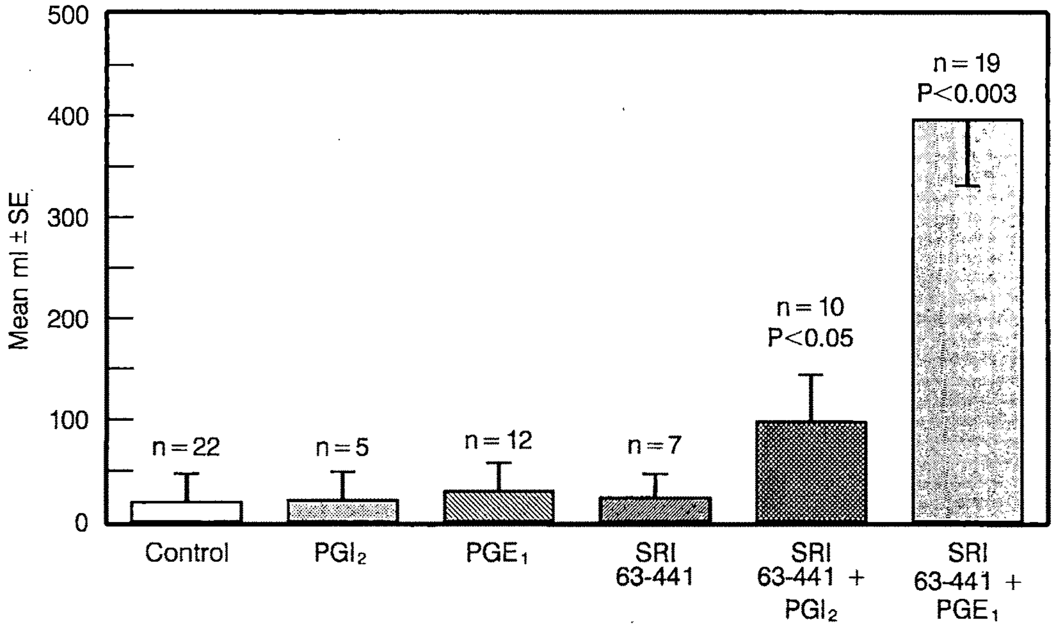


FIG. 2. Function of renal xenografts after pig-to-dog kidney transplantation from experiments described in Figure 1. Results are expressed as total urine output for the entire transplant period (mean milliliters ± SE).

control and treated animals, with a more pronounced gradient evident in the control group. No significant gradient in platelet count between renal artery and vein was observed in Group IV dogs.

The flow studies from six experiments in Group IV (SRI 63-441 + PGE_1 *vs.* PGE_1) are depicted in Figure 5. With the drug combination treatment group, as already evident in renal xenograft survival and function, blood flow to the xenografted kidneys was consistently maintained at significantly higher levels than in the control group (in this case already receiving a vasoactive agent, PGE_1). This is depicted up to 100 minutes after revascularization in Figure 5, since before that time, the PGE_1 alone group had already demonstrated severe diminution of graft flow. However, the combination treatment group maintained a degree of significant flow for most of the duration of the experiment.

Pathologic Evaluation

Microscopically, in the serial experiment, baseline biopsies from both control and treated animals contained normal glomeruli, with normal cellularity, and patent, empty capillary loops (Fig. 6). After reperfusion, both kidneys exhibited progressive obliteration of capillary loops by eosinophilic granular material mixed with red blood cells (Fig. 7). Similar thrombi were found in arteries and arterioles as early as 15 minutes. Tubules

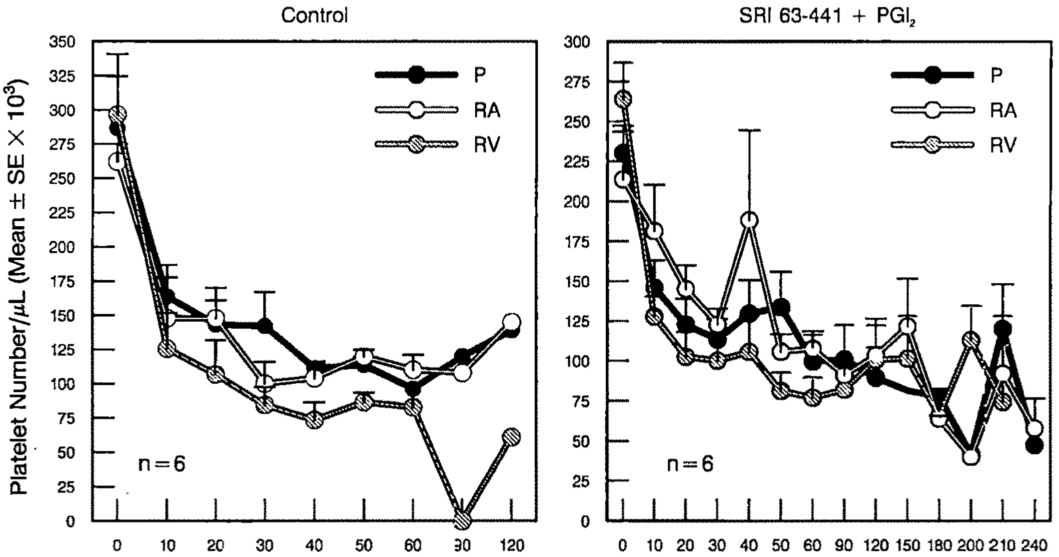


FIG. 3. Platelet counts (mean ± SE) determined for the renal artery (RA), renal vein (RV), and peripherally (P) for six sets of experiments in Group II (SRI 63-441 + PGI_2 *vs.* control).

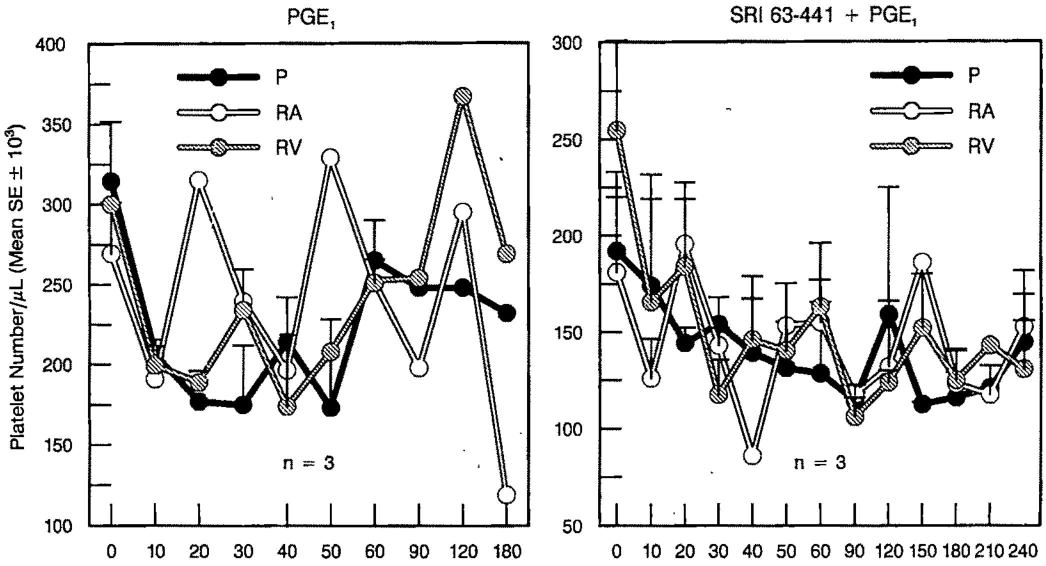


FIG. 4. Platelet counts (mean ± SE) determined for the renal artery (RA), renal vein (RV), and peripherally (P) for three sets of experiments in Group IV (SRI 63-441 + PGE$_1$ *vs.* PGE$_1$).

remained well preserved until 1 hour. There was progressive edema, then congestion, then hemorrhage in the interstitium. At the end stage, when renal function ceased, all specimens showed diffuse thrombosis of glomeruli, arteries, and vasa rectae. There were interstitial hemorrhages and early changes of ATN.

Sequential biopsies. Biopsy specimens at 5, 45, and 90 minutes are shown in Figures 8–10. Qualitatively, the glomerular changes were similar in the control and treated groups. However, the development of glomerular thrombosis proceeded at a slower rate in the treated kidneys. Table 1 shows the results from one epxeriment. The control animal reached end stage with thrombosis in 94% of the glomeruli at 45 minutes, whereas the process reached completion in the treated kidney at 90 minutes. At end stage, red blood cell thrombi were more prominent in the treated kidney (Fig. 10).

Necrosis of tubular epithelial cells was noted in the control kidney with blood in the lumens at 60 minutes. These changes persisted until the end of the experiment.

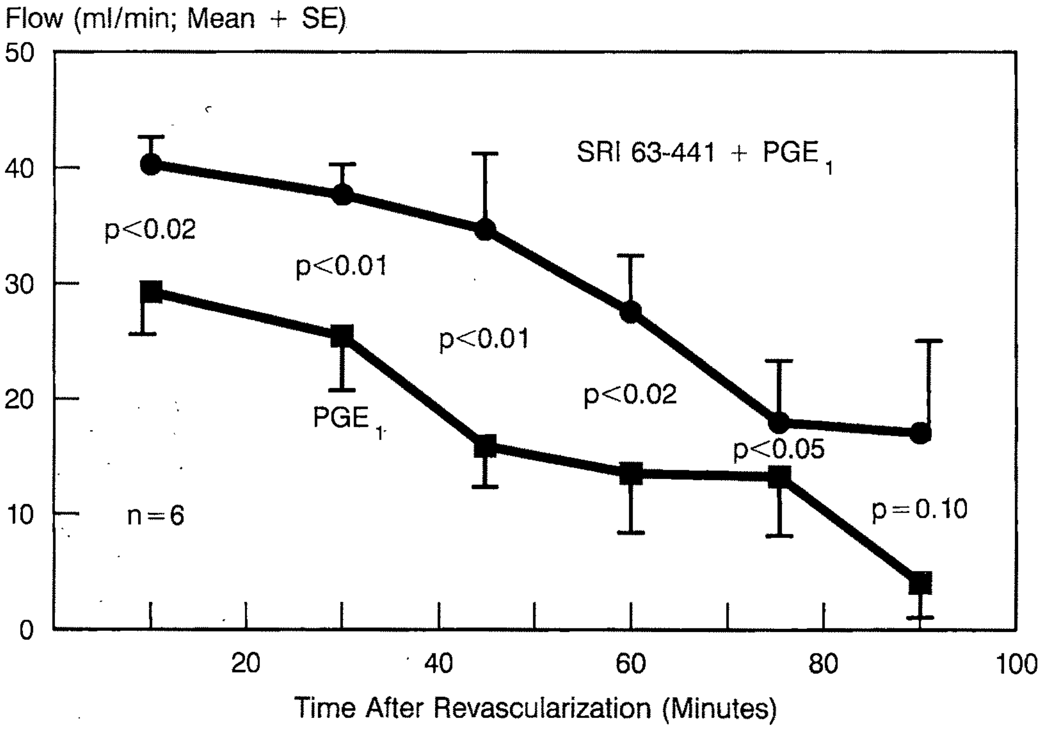


FIG. 5. Electromagnetic flow studies (mean mL/min ± SE) for six sets of experiments in Group IV (SRI 63-441 + PGE$_1$ *vs.* PGE$_1$).

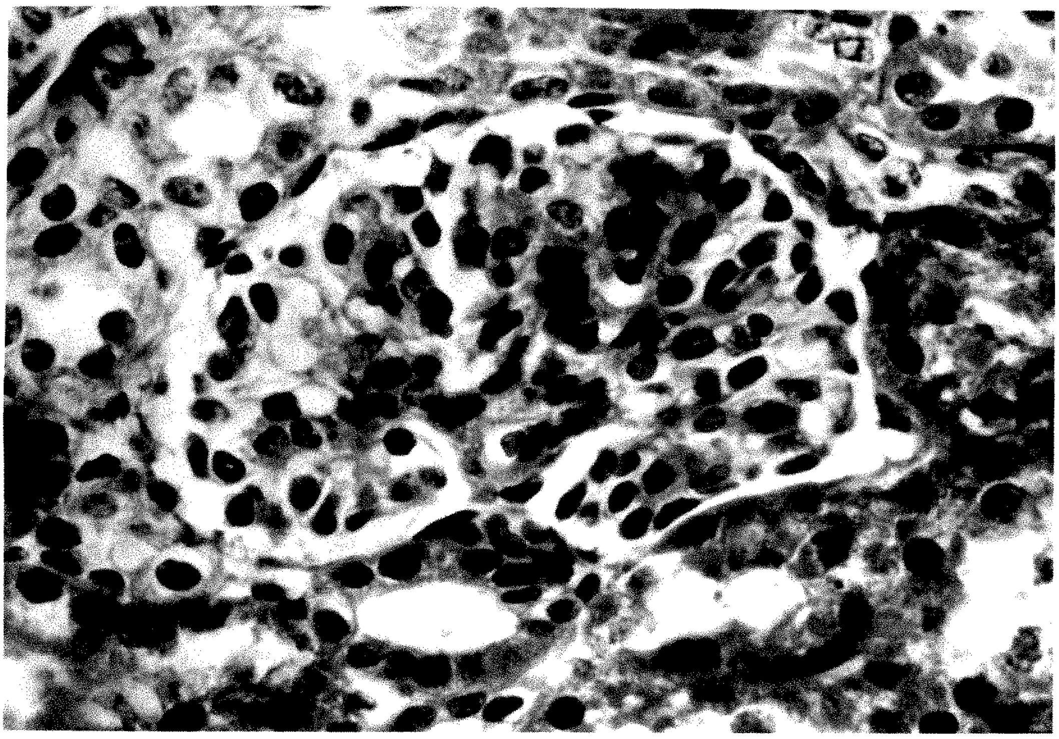


FIG. 6. Baseline biopsy specimen showing normal, empty glomerulus (hematoxylin and eosin, original magnification ×960).

It is important to note that significant necrosis was not noted in the treated kidney.

There was a difference between the two kidneys in the amount and onset of interstitial hemorrhage. Focal hemorrhages were noted in the control kidney at 15 minutes; this progressed to diffuse hemorrhage by 45 minutes and persisted (Fig. 9). In contrast, the treated kidney showed only focal hemorrhages at 30 minutes, and again at 90 minutes. There were no significant differences between the control and treated kidneys with

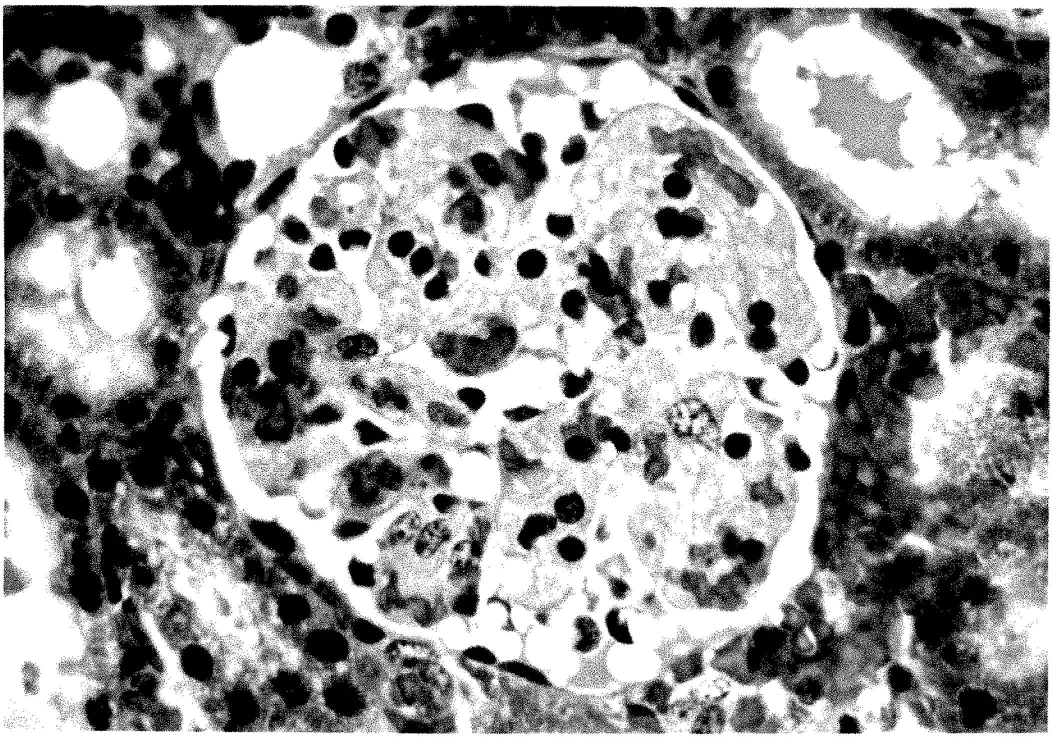
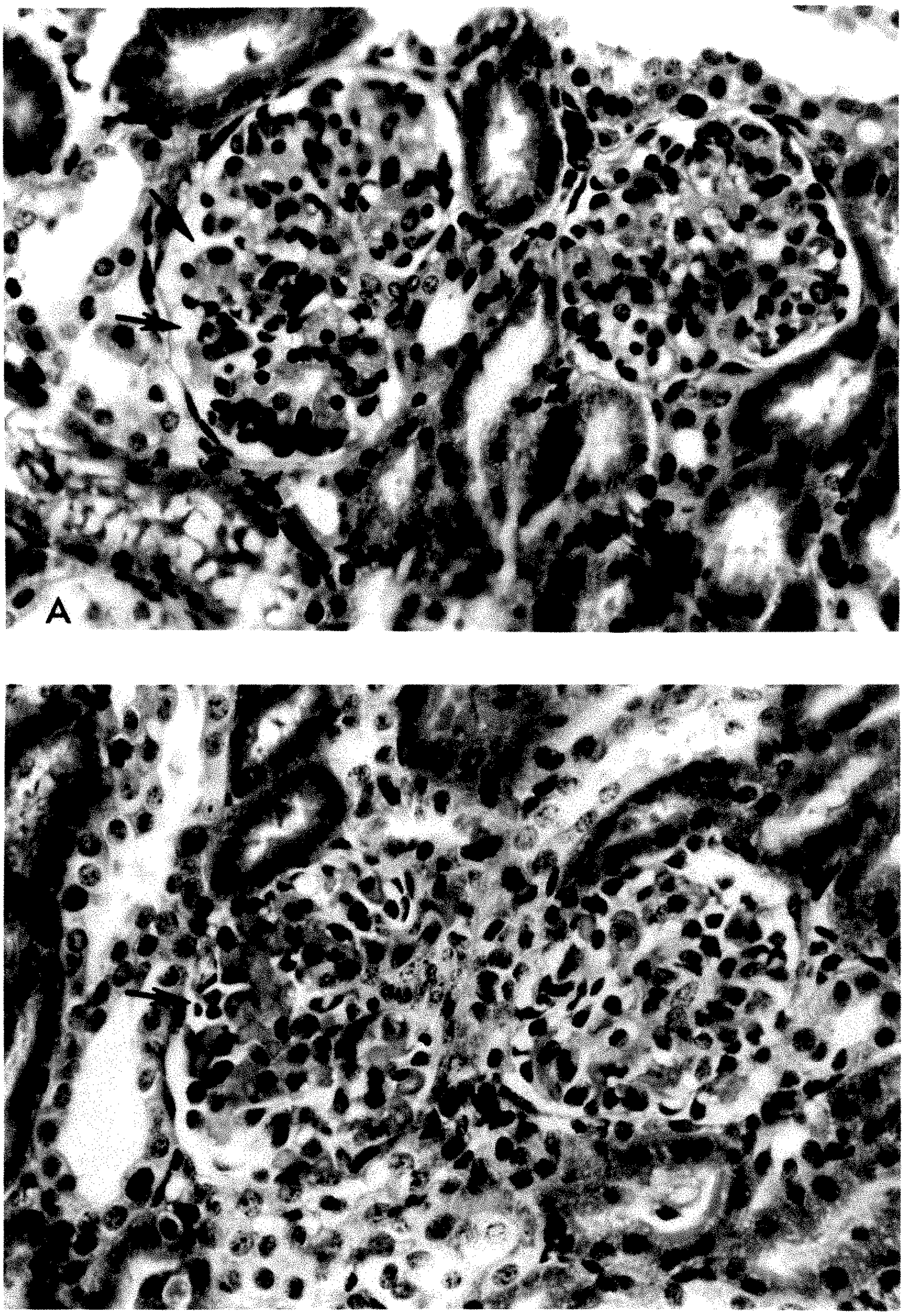


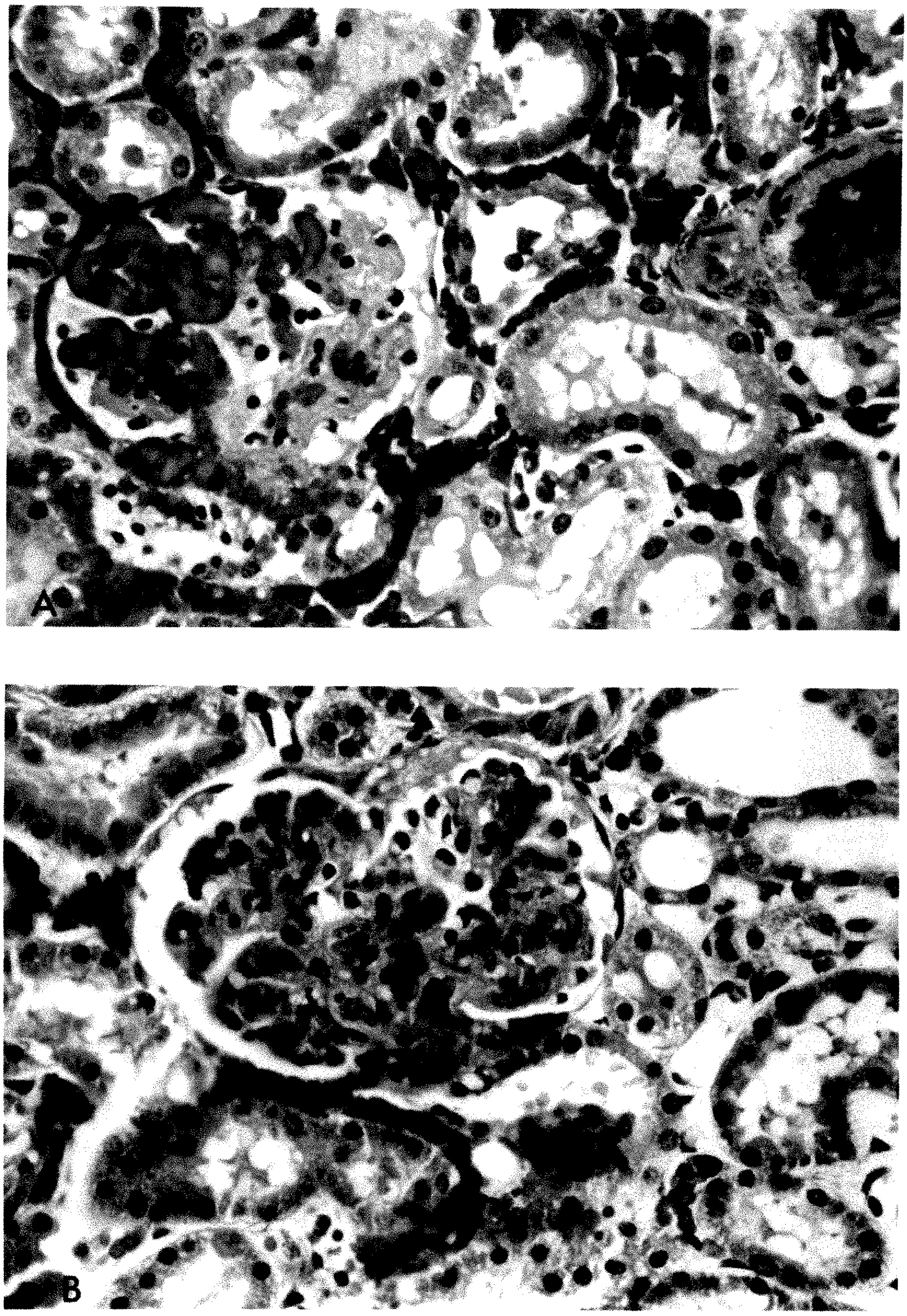
FIG. 7. Glomerulus filled with thrombi composed of RBCs in a pale granular matrix (hematoxylin and eosin, original magnification ×960).



FIGS. 8A and B. Serial study, biopsy specimens at 5 minutes: *A*, control; *B*, treated. Note thrombi in some glomerular capillaries (arrows), and relatively normal tubules and interstitium (hematoxylin and eosin, original magnification ×625).

regard to the presence of thrombi in arteries and arterioles.

End-stage biopsies. The end-stage biopsies obtained after implantation represented a later stage than the sequential biopsies. In these sections, RBCs were a prominent component of the glomerular thrombi in the treated kidneys, whereas in the control groups the thrombi were composed of mostly granular eosinophilic material consistent with platelet-fibrin thrombi, similar to the changes noted in the sequential biopsies. There

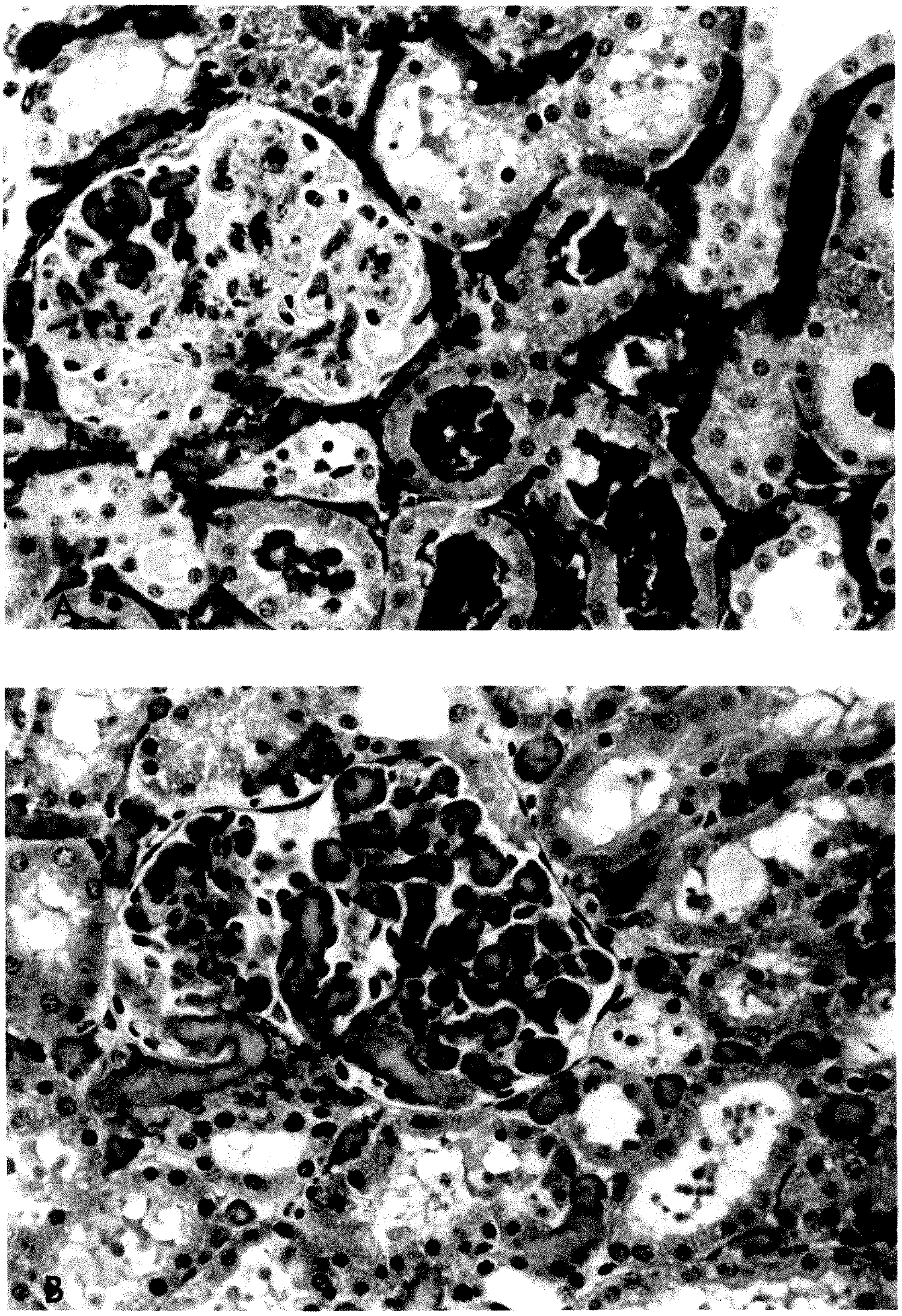


FIGS. 9A and B. Serial study, biopsy specimens at 45 minutes: *A*. control; *B*. treated. Note hemorrhages in the interstitium in the control kidney. Both glomeruli contain thrombi (hematoxylin and eosin, original magnification ×625).

was more interstitial hemorrhage in the treated dogs than in the controls in five cases, and less hemorrhage in four cases. Three of the treated kidneys and none of the control kidneys exhibited up to 20% glomeruli free of thrombi.

Discussion

The candidacy of platelet-activating factor (PAF) as a pivotal biologic mediator in the pathogenesis of antibody-mediated hyperacute allograft rejection has been



FIGS. 10A and B. Serial study, biopsy specimens at 90 minutes: *A*. control; *B*. treated. Note interstitial hemorrhages and blood in the tubules in the control kidney (hematoxylin and eosin, original magnification ×625).

clearly established. *In vitro* studies have demonstrated that PAF is released when endothelial cells are incubated with antibody to cell surface angiotensin converting enzyme.[15] This has important implications for hyperacute rejection, in which the specific initiating event is a transplantation antigen-antibody interaction on the endothelial surface. In a model of hyperacute renal allograft rejection in sensitized rabbits, PAF was identified in the blood effluent from the transplanted kidney, following antibody and complement fixation to the endo-

TABLE 1. *Progression of Histologic Findings in Sequential Biopsies of Control and Treated Kidneys*

	Control			Treated		
Time (Min)	Glomerular Thrombosis (%)	ATN	Interstitial Hemorrhage	Glomerular Thrombosis (%)	ATN	Interstitial Hemorrhage
5	26	0	0	13	0	0
15	69	0	Focal	46	0	0
30	83	0	Focal	60	0	Focal
45	94	0	Severe	73	0	0
60	91	Focal	Severe	80	0	0
75	88	Focal	Moderate	77	0	0
90	78	Focal	Severe	97	Focal	Moderate

thelium of glomerular and peritubular capillaries.[10] No PAF could be detected in rabbits without clinical or histologic signs of rejection. The PAF release was followed by the recruitment of platelets, endothelial sticking, and obliteration of capillaries by platelet-PMN plugs and evidence of cellular degranulation.[10]

The importance of PAF, even in the absence of inflammatory cells, was demonstrated in a model of *ex vivo* perfusion of the rabbit heart with transplantation alloantibodies.[16] The release of PAF followed bradycardia, conduction arrhythmias, decreased coronary flow, and cessation of heart action. These alterations in cardiac function and, moreover, the release of PAF, were prevented by complement inactivation. PAF itself induced a negative inotropic effect and reduction of coronary flow in isolated guinea pig heart muscle by a direct action on the Ca^{++} slow channel. Moreover, the injection of synthetic, purified PAF into the renal artery of rabbits reproduced a pathologic picture identical to that seen in a Shwartzman reaction of the kidney.[17] The pathophysiology of hyperacute renal rejection in humans was originally described as a Shwartzman reaction.[1]

The nonspecific effector inflammatory cascade that ensues once an antigen-antibody reaction has initiated hyperacute rejection has served as the target for therapeutic intervention by many different approaches. Classically, the platelet-coagulation system has been considered to be the most important and has received the greatest attention. These therapeutic modalities have included heparin, aspirin, dextran, citrate, defibrinating agents, cobra venom factor, induction of thrombocytopenia by antibodies etc., and various prostaglandins.[18-21] All these approaches have been either too toxic or the results too inconclusive to be accepted for generalized use.

The difficulty in overcoming the inflammatory process in hyperacute rejection and in explaining the discrepancies in therapeutic results rest not only in the complexity of the biologic reactions, but also in their resiliency and redundancy. That is, there are numerous alternative mediator pathways that can backup the same set of functions. Thus, the inhibition of one arm of an inflammatory reaction can easily be replaced by the release of other inflammatory autocoids with complete mediation of a disease process. PAF may represent somewhat of an exception to this hypothesis, because of its potency and its unique potential for mediating almost every aspect of acute inflammatory reactions. Nonetheless, the argument for polypharmaceutical therapy of hyperacute rejection is clear.

The current study represents the first known report describing the therapeutic efficacy of a receptor antagonist of PAF in any *in vivo* model of hyperacute rejection. These studies not only lend further support to the prominent role of PAF in the regulation of the inflammatory response leading to hyperacute rejection, but also introduce a new and potentially significant therapeutic approach to this entity. The agent used in these studies, SRI 63-441, is currently the most potent and specific PAF receptor antagonist available. It represents a family of compounds that can be synthesized and modified to meet desired specifications, *i.e.,* an oral compound recently has been produced.

At the single dosage and schedule of SRI 63-441 evaluated in these studies, inhibition of PAF alone was not sufficient to improve renal xenograft survival or function, although a trend did exist. From studies in rats and other recent studies in dogs, we have determined that the critical consideration for the efficacy of SRI 63-441 is to administer it at a much higher dose and before revascularization (unpublished data). However, the addition of either one of two prostanoids, PGI_2 or PGE_1, resulted in a synergistic response and a manyfold increase in renal xenograft survival and function. Although a higher dosage and more appropriate scheduling of SRI 63-441 may improve the effectiveness of single drug therapy, the need for multiple drug treatment eluded to above may be necessary to adequately modulate this violent inflammatory process.

There are many reasons for choosing PGI_2 and PGE_1 as complimentary agents to SRI 63-441. They both inhibit platelet function by stimulation of receptor-coupled adenylate cyclase and increase intracellular cAMP, a receptor mechanism different from that required for SRI 63-441 inhibition.[22] To varying degrees, they both exhibit other properties that establish them as excellent therapeutic candidates for such inflammatory processes. These biological activities include vasodilatation, fibrinolytic action, inhibition of the generation of certain deleterious metabolites of the arachidonic acid cascade, inhibition of oxygen-free radical generation, and the property known as cytoprotection.[22] Moreover, both these prostaglandins have been evaluated in other models of hyperacute rejection. Treatment with PGE_1 prolonged hamster-to-rat cardiac xenograft survival.[23] PGI_2 administration significantly prolonged kidney survival in both a model of hyperacute renal allograft rejection in presensitized dogs and in cat-to-dog xenografts,[21,23] but had no effect on guinea pig-to-rat cardiac xenograft survival.[23] Neither PGI_2 nor PGE_1, when administered alone as a constant infusion without combination SRI 63-441 treatment, had a significant effect on pig-to-dog renal xenograft survival or function as described in our studies. Furthermore, the therapeutic effectiveness of these prostaglandins in combination with SRI 63-441 was evident only when they were infused intra-arterially; peripheral administration of prostaglandins did not exhibit synergism with SRI 63-441 (unpublished results). This is most likely due to inactivation of prostaglandins as they pass through the lungs.[22]

The pig-to-dog renal xenograft model evaluated in these studies probably represents the most severe animal model of hyperacute rejection known. Rapid and violent kidney rejection is the rule and there have been only a few reports of successful abrogation of this process. Shons and Najarian reported a significant increase in pig renal xenograft survival from a mean of 5 minutes in controls up to a mean of 45 minutes in dogs treated with a variety of antiplatelet agents.[19] Merkel et al. reported renal xenograft survival times of 120, 90, and 180 minutes in three dogs that had preoperative plasmapheresis.[24] Kux et al. reported a mean rejection time of 85 minutes in 15 kidneys treated with intra-arterial citrate infusion; these experiments were limited by significant toxicity.[20] The control xenografts for the latter two sets of experiments rejected in less than 10 minutes.[20,24]

Consistent and reproducible results were achieved in the same model in the current studies by combining SRI 63-441 with either PGI_2 or PGE_1. Pig kidneys surviving for 3–4 hours were consistently achieved with maintenance of good urine output in all combination treatment groups. There were three kidneys in this series of experiments that functioned satisfactorily for 6–9 hours. These results compare most favorably with any previous reports of this particular model.

Although the differences in the pathologic evaluation of treated and control animals were subtle, there is no doubt that on serial histologic examination, treated animals demonstrated a delay in the evolution of the final morphologic deterioration. Futhermore, the end-stage histologic examination in treated kidneys demonstrated an overall amelioration, albeit minor, of the entire pathologic process. The histologic findings correlated with the clinical course. The significant improvements in renal xenograft survival and function were also paralleled by a significantly delayed diminution in renal artery blood flow and a significantly improved gradient of the plätelet count between renal artery and vein in combination treated animals.

Emphasis on platelet counts and gradients may not be as important as once believed. It is clear that although PAF is a potent modulator of platelet aggregation and release, it can promote the pathophysiologic process of hyperacute rejection by various other pathways.[8–12] Furthermore, rats with a defect in platelet aggregation exhibited the same time course and morphologic features of hyperacute cardiac rejection as in normal rats,[6] and platelet aggregation was demonstrated not to be essential in a model of renal xenograft rejection.[25]

In summary, these studies further confirm the central role of platelet-activating factor in the inflammatory cascade that destroys kidneys undergoing hyperacute rejection. Furthermore, this report introduces a novel, reproducible, and potentially effective therapeutic approach to this difficult problem, which relies on a better understanding of the basic pathophysiologic process of inflammation and which utilizes as its basis, a synthetic receptor antagonist that specifically inhibits the potent and unusually diverse spectrum of biologic activities of one of the key mediators of classical inflammation.

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DISCUSSION

DR. EDWIN W. SALZMAN (Boston, Massachusetts): This is a very interesting paper, but there are several concerns I have about some of the details of the use of the inhibitor of platelet activating factor (PAF).

One of the most striking things about PAF is its species specificity. There is evidence, for example, in humans, although perhaps not in rabbits or in dogs, that the action of this agent is mediated through cyclo-oxygenation of arachidonic acid, and ultimately through the generation of prostaglandin endoperoxides and thromboxanes. These processes are totally blocked by aspirin, and I wonder if the observations made on these animals would be relevant in humans. Might one not expect that in humas the effect of aspirin would be as great as the effect of the specific inhibitor of PAF?

The second question relates to the dose of prostacyclin that was used, which is about 40 times the maximum tolerable dose in humans. Is there reason to believe that the findings with such a large dose of this prostaglandin would be relevant to the human situation?

Finally, we have seen that the histology after the graft finally failed was different in the animals treated with the antagonist to PAF and with prostacyclin. This is a situation in which there is virtually total paralysis of platelet function, and I wonder if the author would comment further on the presumed difference in mechanism of graft failure in the animals receiving the PAF antagonist.

DR. P. O'LEARY (Dallas, Texas): I enjoyed your paper very much. I have one question.

It looked to me as though the platelet count did not fall as far in the treated animals, but the extraction arterial to venous was as great. I wonder if you attempted to quantify the extraction of platelets as they passed through the kidney.

DR. M. WAYNE FLYE (St. Louis, Missouri): You state that there is abrogation of the hyperacute rejection, but in fact, the graft still fails at about 400 minutes. Your histology shows some clearing; however, it does not show the expected deposition of fibrin and platelets onto the endothelium. Would you comment on why the graft fails even though there is some prolongation of survival?

DR. COURTNEY M. TOWSEND, JR. (Galveston, Texas): That was a very nice study. There was a lot of work in it. It was very well presented. I wondered why you had to give the prostaglandins in addition to the PAF antagonist in the pig-to-dog model and did not apparently do that in the rat model.

DR. WILLIAM E. NEVILLE (Newark, New Jersey): This was a beautifully presented paper and their results were stimulating.

As I look back at what our group did in the 1960s and early 1970s on heterologous cardiac transplants in animals, I realize now that I should have continued with this work. However, we did not have the drugs that today seem to prevent early rejection between certain heterologous animals. We initially inserted the hearts of calves, sheep, goats, and pigs orthotopically into dogs on cardiopulmonary bypass using only Ringer's lactate to prime the pump oxygenator. The hearts were initially pink and contracting but deteriorated rapidly. Histologic and electromicroscopic studies showed microcirculatory red cell agglutination without fibrin despite platelet aggregation and inflammatory reaction. We then reversed the experiements and placed dog hearts into calves, sheep, goats, and dogs using the same technique. All of the transplanted hearts were easily defibrillated and adequately maintained the circulation until the dogs were killed hours later. Microscopic examination of the dog hearts showed few ultrastructural changes. The capillaries were invariably patent with no significant alterations of the endothelial cells. The myocardium only showed some patchy interstitial edema and slight mitochondrial swelling and glycogen depletion. The reason for this striking contrast in the two groups was not clear; but we reasoned and published that it might have something to do with the disproportion between the red blood cells and capillaries, thus disregarding an antigen–antibody reaction.

I would like to see the group from Pittsburgh use this relatively new drug alone or in combination with other antiplatelet drugs to see whether the Schwartzman reaction could be prevented in xenograft hearts inserted into dogs on cardiopulmonary bypass. We definitely need heterologous organs for transplantation but we do have much to learn regarding the use of these organs in humans.

DR. NICHOLAS L. TILNEY (Boston, Massachusetts): I also enjoyed the paper very much. We have been looking at a slightly different model in a rat heart graft system, so-called accelerated rejection that occurs about 36 hours after transplantation instead of in a few minutes as occurs in a presensitized rat.

In the beginning of the process, we found more or less what these authors have found, a very accelerated rejection that is primarily a humoral event. There are a few infiltrating cells; however, most of which are activated cells bearing interleukin II receptors on their surfaces.

We can abrogate this early rejection and get grafts out to about 3 or 4 weeks using either cyclosporine in various doses or monoclonal antibodies directed against the interleukin 2 receptors. Regardless of treatment, the grafts ultimately reject at about 3 weeks, but the primarily humoral rejection has been converted to a primarily cellular one, an extremely interesting observation.

I would like to aske the authors whether they had a chance to look at the infiltrating cell populations during the time their grafts are still viable, because I believe they will find these are a very interesting cell subgroup and mostly interleukin 2 receptor positive.

DR. LEONARD MAKOWA (Closing discussion): I would like to thank all the speakers for their helpful comments and interesting questions.

Many of your questions have concentrated on the importance of platelets in the overall process of hyperacute rejection and, therefore, I will try to cover these together. There is no doubt that platelets play a role in this process. However, over the last 20 years, since this entity was described, there has been a hangup on the importance of platelets and the major role that they play in the overall pathophysiology of this process. Many investigators had demonstrated platelet consumption by kidneys that were undergoing hyperacute rejection by studying platelet gradients between the renal artery and vein of these kidneys. Histologically, platelet accumulation and aggregation was a major feature of the final pathologic process. Nonetheless, it is now clear that the role and the importance of platelets in this process is just one small component of a much bigger picture, and that the entire evolution of hyperacute rejection must be redefined.

There is considerable evidence in the literature that indicates platelets are not the sole or major contributor to the process of hyperacute rejection. These experiments have demonstrated that the identical clinical and histopathologic entity of hyperacute rejection can occur in the face of platelet depletion, or in animals with a hereditary deficiency of platelet function. In fact, it now appears that other cellular components, especially the neutrophil, may play an equal or even more important role.

Currently, hyperacute rejection must be considered the end product of a set of complex nonspecific inflammatory reactions, which are initiated by a specific antigen–antibody reaction. I tried to demonstrate some of these contributory inflammatory arms in the first slide, and to emphasize their resiliency and redundancy. Thus, many alternative backup inflammatory systems can result in the same set of functions and final pathologic process. The relative importance of each of these inflammatory pathways is as yet unknown, and furthermore, the relative importance of blocking or inhibiting the biologic activity of any one specific mediator remains to be fully defined.

I must re-emphasize that the designation of the mediator that we are discussing today, as platelet activating factor, is a misnomer. PAF plays a role in most of the classical mediator systems of the acute inflammatory process, in the generation of arachidonic acid metabolites, and in the generation of oxygen free radicals, etc. Although PAF is one of the most potent inducers of platelet aggregation and release, and thus by this mechanism plays a contributory role in hyperacute rejection, there is now clear evidence that establishes PAF as a central candidate in the overall evolution of this inflammatory process and as a key biological mediator in the pathogenesis of antibody-mediated hyperacute allograft rejection. This lead to our hypothesis that antagonism of PAF-induced reactions offered a potential therapeutic approach to this entity by inhibiting many of the key inflammatory pathways.

It is true that one of the actions of the PAF antagonist is to inhibit the cyclo-oxygenase pathway, thereby inhibiting the formation of various biologically active autocoids of the arachidonic acid cascade, as well as interfering with platelet function. Aspirin exhibits these same specific properties, but does not influence the numerous other inflammatory pathways as the PAF antagonist can. Dr. Najarian's group described a set of elegant experiments in Transplantation Proceedings in 1974, where the effect of aspirin was evaluated in this same model of pig-to-dog renal xenografts. They found that the mean graft survival time of 5 minutes in control animals was increased to 21 minutes by aspirin treatment. In fact, the addition of dextran to aspirin treatment further increased the mean graft survival time to 45 minutes. At that time, these were considered significant results. Obviously, the numerous backup pathways could overcome this single-pronged approach in such a severe xenograft model. That is why we have initially taken the approach of multipharmaceutical therapy, and demonstrated a synergistic effect by combining a prostaglandin with the PAF antagonist.

In our studies, we consistently achieved renal xenograft survival of 3 to 4 hours and in a few cases achieved 9-hour survival. These results significantly surpassed previously published reports using this same pig-to-dog model, which we believe is probably the most severe experimental model of hyperacute rejection known.

I agree that the dose of prostacyclin that we have reported in these particular studies today was too high. We did observe some hypotension in these animals. Subsequently, we have repeated these studies using a much lower dose of prostacyclin and have achieved the same efficacy. Similarly, for prostaglandin E_1, we have used dosages as low as 0.01 μg/kg/min, which is well tolerated in humans.

One of the problems with the studies that I have described to you today, is that based on our subsequent rat studies, we probably were not using enough of the PAF antagonist. In these studies, we used 5 mg/kg. From subsequent studies of hyperacute rejection using a model of heterotopic cardiac transplantation in hypersensitized rats, we have learned two critical points. A much higher dose of the drug can and should be given, and the dose given before revascularization is the key for efficacy. In fact, we have demonstrated significant prolongation of cardiac allograft survival in this model using 15 or 20 mg/kg given 4 minutes before revascularization.

It appears that it is much easier to overcome this process in the rat heart model using the PAF antagonist alone. As I already mentioned, this may be due to a dosage and scheduling inefficiency in the xenograft model reported today. However, in the xenograft model we are probably dealing with a much more potent initiating immunologic reaction. Therefore, the trigger for this overall process may be different, and may require a modified therapeutic approach, *i.e.*, that of utilizing polypharmaceutical therapy. Alternatively, we must appreciate the contributions of the different microvasculatures of the kidney and the heart.

I agree completely with Dr. Tilney, that the importance of the rat model should be emphasized. Unfortunately, these initial studies were presented in the closing two slides, but it is apparent that in the rat model, we have converted the process of hyperacute rejection into one of classical cell-mediated rejection. We have not as yet had the opportunity to characterize the infiltrating cells in the hearts that underwent classical rejection. We are currently in the process of combining the PAF antagonist with standard immunosuppression in this model. We certainly agree that the combination of the ability to overcome the inflammatory process resulting from the initial antibody insult and of controlling cell-mediated rejection with appropriate immunosuppression, at least in the homograft rat heart model, may allow us to overcome the entire process of hyperacute rejection.

Long-term Evaluation of Aortic Valvotomy for Congenital Aortic Stenosis

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Aortic valvotomy (AV) for relief of congenital aortic stenosis (AS) is a palliative operation, and the purpose of this study was to determine the long-term benefit. After analyzing the symptoms at time of operation, 177 patients were separated by age at AV: newborns (1–14 days) 26, infants (2 weeks–1 year) 19, and children (≥1 year) 132. The newborn with critical AS typically presents with severe cadiac failure and the infant with moderate failure, whereas children may be asymptomatic. In the newborn group, final diagnosis has been made exclusively by noninvasive cardiac echogram since 1984. The presence of a hypoplastic left ventricle (HLV) and/or endocardial fibroelastosis (EFE) are the most important determinants of mortality. Operative survival was 11 of 13 (85%) in the newborn group if HLV/EFE were not present. No operative deaths for AV occurred after 1965 in children. When present, a preoperative electrocardiographic strain pattern resolved in 80% of patients. Of 33 reoperations (21%), four were required 1.0 (0.5–2) years later for newborns, five were required for infants 7.2 (1.5–20) years later, and 24 were required in children 11.0 (1.5–25) years later. These included 10 repeat valvotomies and 23 aortic valve replacements (AVRs) with a 91% survival rate. In summary, although valves of patients with congenital AS are morphologically abnormal, valvotomy is beneficial. It was found that (1) the operative survival rate has been 100% over the past 20 years for children and currently is greater than 80% in newborns in the absence of HLV/EFE; (2) reoperation rate is higher in newborns and infants; (3) benefit was shown by a sharp decrease in obstruction initially and improved ECG later; (4) long-term follow-up revealed a subset of patients who are asymptomatic and have only mild residual obstruction over 20 years after AV.

AORTIC VALVOTOMY (AV) for congenital aortic stenosis is a palliative operation, and considerable valve deformity persists despite relief of obstruction. Nevertheless, AV is widely performed because of the poor outlook for patients with severe stenosis. Althogh many series report initial benefit, longer follow-up has shown an increasing reoperation rate, attrition by late deaths, and return of symptoms in a significant number of patients.[1-5] One recent series has even concluded that all patients will require reoperation within 20 years of the initial valvotomy.[6] A contributing factor to this pessimistic outlook may be that previous follow-up measurements of left ventricular–aortic (LV–Ao) pressure differences by cardiac catheterization were done almost exclusively on symptomatic patients.[1-6] These studies showed significant residual pressure gradients, and the conclusion has been drawn that inexorable and relatively rapid aortic valve deterioration is the fate of these patients. To determine if this conclusion is correct, evaluation of an entire group of patients who had undergone AV would be necessary.

The purpose of this study, therefore, was to obtain this long-term follow-up data. Because AV under direct vision was first performed at this institution in 1955, a long-term analysis of these patients was possible. We attempted to obtain studies on all patients, whether asymptomatic or symptomatic, who had not had cardiac catheterization or had an echocardiogram done within the last 2 years. These data would allow us to examine several important questions, including (1) whether or not the operative approach and results have changed over the past 30 years, (2) the clinical spectrum and corresponding prognoses of these patients and, most importantly, (3) the long-term benefit of AV for a patient with significant congenital aortic stenosis.

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Methods

Patient Population

During the period under review (December 2, 1955 to November 30, 1986), 177 patients under 25 years of age had aortic valvotomy for congenital aortic stenosis. There were 124 males and 53 females. All AVs were done under direct vision using a transaortic approach, and all but one, the first patient in this series, were performed on cardiopulmonary bypass. The first patient had direct vision valvotomy during a period of hypothermic inflow occlusion.[7] Review of the operative technique has shown relatively little variation over the period under study. Using hypothermia with or without cardioplegic arrest, the aortic incision typically was extended toward the noncoronary sinus. Evacuation of the left ventricle provided visualization of the valve and revealed the commissural fusion. Usually (see Results), a bicuspid aortic valve was encountered with the major fused commissure located anteriorly. Care was taken to evenly divide the fused commissural ridge, and the incision was usually carried to the annulus itself. When a unicommissural valve was encountered, only two incisions were made in an attempt to create a bicuspid valve. Only in the rare instance of a clearly tricuspid valve were three incisions made.

Associated Cardiac Defects

There were 67 significant associated cardiac defects (excluding patent foramen ovales) among the 177 patients. A patent ductus arteriosus occurred 23 times. Coarctation of the aorta was present in 17 patients, a subaortic membrane was present in two patients, a ventricular septal defect was present in two patients, and a coronary ostial membrane was found in one patient. Significant mitral regurgitation was present in 18 patients and was more prevalent in the younger patients. Among newborns, 11 of 26 (42%) had significant mitral regurgitation or stenosis, including four patients with a dysplastic mitral valve.

Diagnosis

In all except six cases, the clinical diagnosis was confirmed before operation either by cardiac catheterization with direct pressure measurements or echocardiography with doppler based pressure estimations. By cardiac catheterization, pull-back measurements yielded peak-to-peak LV–Ao systolic pressure differences. This pressure difference was commonly used as the gradient for determining preoperative status and follow-up results. The mean pressure differences were used for calculation of the valve area by the Gorlin formula. More recently, echocardiography including doppler determinations have been increasingly used to estimate the LV–Ao pressure differences. With echocardiographic analysis, the mean systolic pressure differences were used rather than the peak-to-peak instantaneous gradients that tend to overestimate the obstruction.[8]

Echocardiographic techniques were also used to assess the left ventricular chamber size and determine if endocardial fibroelastosis (EFE) were present to assess the adequacy of the left ventricular chamber. Early in the series, a hypoplastic left ventricle (HLV) was diagnosed when the transverse diameter of the left ventricle fell below the normal range. More recently, the contours of the chamber have also been taken into account. An HLV tends to have a spherical cavity without the usual greater longitudinal dimension. Currently, if the transverse diameter is less than 12 mm and the LV cavity spherical in contour, then the newborn is judged to have an HLV.

In the presence of significant EFE, virtually the entire endocardium including the papillary muscles of the LV are echo reflective to a depth of approximately one fourth of the wall thickness. Newborns meeting these criteria were judged to have EFE. Before the use of echocardiography, this diagnosis was made only at postmortem examination.

Electrocardiographic Analysis

A standard 12-lead electrocardiogram (ECG) was used to provide additional information on the severity of obstruction. Patients over 1 year of age were judged to have left ventricular hypertrophy (LVH) if the R-wave in V-6 was 25 mm or greater or the S-wave in V-1 was 25 mm or greater in height. The diagnosis of strain was made by T-wave flattening or inversion or S-T depression in the lateral precordial leads.

Patient Follow-up

There were 22 operative deaths; therefore, 155 patients were available for potential follow-up study. Follow-up for this study began with analysis of patient records from the University of Minnesota and outside records and patient contact by questionnaire and telephone. By these methods we determined there were 12 late deaths, six patients who currently are lost to follow-up, and two patients could not be traced after discharge. Unfortunately, the first patient, now over 31 years post AV, is among those currently lost to follow-up. Total follow-up is 1865 patient years with mean follow-up of 12.1 years (range: 0.5–29.5 years). This includes 39 patients followed up for more than 20 years and 18 patients followed up beyond 25 years. Only nine patients were followed up less than 10 years, although 51 patients

TABLE 1. *Symptoms of Patients by Age Before First Operation*

Symptom	1–14 Days	15 Days–1 Year	Over 1 Year
Severe cardiac failure	25 (96%)	0	0
Moderate cardiac failure	1 (4%)	18 (95%)	4 (3%)
Asymptomatic	0	1 (5%)	63 (47%)
Exercise intolerance	—	—	45 (34%)
Angina	—	—	10 (8%)
Syncope	—	—	9 (7%)
Palpitations	—	—	1 (1%)
Total	26	19	132

have had a valvotomy less than 10 years before the time of analysis.

Follow-up was accomplished when the patient's history and current condition was determined by return of the mailed questionnaire. The questionnaire was supplemented whenever possible by direct contact and review of current medical records. The patient was considered studied when the LV-Ao pressure difference was determined either by echocardiogram or cardiac catheterization. When the interval from the previous study exceeded 2 years, a repeat study was strongly encouraged. Although this has not been accomplished in all cases, postoperative pressure data are now available up to 28 years after valvotomy.

Statistical Analysis

Objective data were calculated as the mean ± SD. Standard actuarial techniques were used to calculate survival, freedom from reoperation, and freedom from symptoms. Pressure differences (LV-Ao) were calculated using paired data for the individual patient and both the range and standard deviations determined.

Results

To subdivide the obviously broad clinical spectrum of congenital aortic stenosis and allow a more meaningful analysis, several parameters were reviewed. The high mortality of AV in infancy and the very low risk in children older than 1 year has long been recognized.[3,9] Further subdivision would seem appropriate because, in general, a 1-day-old infant is at much greater risk than is a 1-month-old infant. We analyzed the symptoms at the time of first operation to determine how this subdivision should be made. An age categorization emerged that seemed to correlate with clinical severity and operative result (Table 1).

Patients were judged to be in severe cardiac failure if two or more factors were present, including clinical shock, need for preoperative blood pressure support, assisted ventilation, or acidosis. We found 25 of 26 patients operated on from 1–14 days of life were in severe cardiac failure. Within this group, 22 of 26 patients were operated on from 1–7 days of age.

Moderate cardiac failure as judged by physical examination, chest x-ray examination, and the need for diuretics and/or digitalization was characteristic of infants operated on from 15 days to 1 year of age. For children 1 year of age and older, 47% were asymptomatic, and if symptoms were present, they were suggestive of later developing problems of aortic stenosis. Analysis, therefore, was made on these three age groups: newborns (1–14 days of age), infants (15 days–1 year of age), and children (over 1 year of age).

Valve morphology was tabulated from the operative reports, and the difficulties of this determination at the time of surgery must be acknowledged. The nomenclature of Edwards[10] was used regarding unicuspid, bicuspid, or tricuspid congenital aortic stenosis. As a reflection of the increased severity of the valve abnormality in the younger patient, 16 of 26 (62%) newborns had a unicuspid valve, whereas 7 of 19 (37%) infants and only 9 of 132 (2%) children had this deformity. A bicuspid valve was the most common type of deformity (76% overall) and the tricuspid valve was relatively rare (6% overall).

Operative survival has continued to increase during the study. No early deaths were recorded in children since 1965 or in infants since 1977. The newborn group, however, had a low (12 of 26 or 46%) overall survival rate, as has been frequently reported.[3,9] Because of this high mortality, further analysis was made to determine the risk factors. Analysis revealed the presence of a hypoplastic left ventricle (HLV) or endocardial fibroelastosis (EFE), and these were associated with an extremely poor prognosis. No patient (0 of 7) with HLV and EFE and only one of six (17%) patients with EFE alone survived the operation. In contrast, with an adequate LV and without EFE, survival was 11 of 13 (85%) patients. The improved recent survival rate may also result in part from using echocardiography exclusively since 1984 to confirm the preoperative clinical diagnosis. No newborns have been subjected to preoperative cardiac catheterization since 1983, which may mean they reach the operating room in better condition.

Both the newborn and infant survivors were burdened with a much higher reoperation rate than the patients over 1 year of age who had AV. For the combined newborn-infant group, 11 reoperations were required during 153 patient years of follow-up for a reoperation/patient year ratio of 0.072. For children, however, the ratio was only 0.013 (22 of 1712). The reoperation rate for the newborn-infant group, therefore, was 5.5 times that for children.

Children and young adults (1–25 years of age) comprised the largest group (132 patients), and a longer fol-

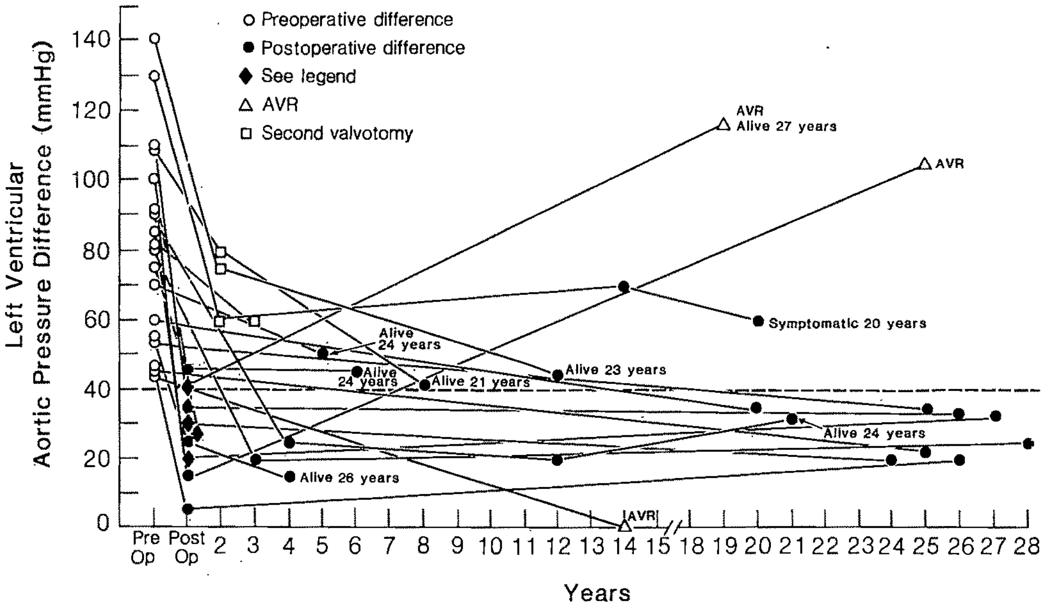

FIG. 1. Paired LV-Ao pressure differences for patients 1 year of age or older undergoing aortic valvotomy. Not all patients had intraoperative measurements and these patients (◆) have a postoperative measurement estimated from follow-up studies. For patients without recent follow-up studies, their survival since valvotomy is indicated.

low-up period was possible. Paired data were used to assess the initial relief of obstruction by AV. The preoperative value was compared with the early postoperative value, usually determined at the time of operation by direct pressure measurement. We subdivided the patients into those with moderate (<75 mmHG) or severe (>75 mmHg) preoperative LV-Ao pressure differences to determine if AV was as effective in relieving severe stenosis as moderate stenosis. Where paired data were available, AV was nearly as effective in releiving severe stenosis (from 103 ± 24 mmHg to 19 ± 17 mmHg, N = 29) as moderate stenosis (from 53 ± 9 mmHg to 13 ± 10 mmHg, N = 18). The mean absolute and percentage reduction, consequently, was greater in the group with severe stenosis.

Preoperative ECGs were obtained in 104 children (79%). Fourteen (13%) had normal ECGs, 55 (53%) had LVH, and 35 (34%) had LVH with strain. Follow-up ECGs done 6.3 years (range: 0.25–27 years) after AV revealed improvement in 52 (58%) patients with preoperative LVH or LVH with strain. In addition, the strain pattern in 28 patients (80%) had resolved after AV, including 12 patients (34%) who had normal ECGs.

Long term follow-up of the LV-Ao pressure differences was possible in 17 patients (Fig. 1). Among these patients, three had an AVR 4, 17, and 25 years after AV and a fourth patient died suddenly at 25 years and, presumably, should also have had a valve replacement. Nine patients, however, 20–28 years after initial AV, are without pressure evidence of a significant increase in the degree of obstruction.

Actuarial analysis provides a prediction of outcome for the patient population. The actuarial survival, freedom from reoperation, and freedom from symptoms are presented in Figure 2. Bacterial endocarditis was uncommon in our series (5 episodes, no deaths) and was not subjected to actuarial analysis.

Because of the many difficulties involved in a study of this type, including late attrition, patients lost to follow-up, and inability to obtain late LV-Ao pressure studies, a compilation of the group is also very informative. The fate of patients (≥1 year of age at operation) who had aortic valvotomy 20 or more years ago are presented in Table 2. The original patient group numbered 58 patients, and four were excluded from analysis. There were three postoperative deaths for technical reasons involving cardiopulmonary bypass early in the series. These patients were among the first operated on for this lesion and there is general agreement that the mortality in this patient group now approaches zero. These patients were, therefore, excluded from analysis. The fourth patient lived far away from the hospital and returned home after discharge. No follow-up information was obtained; therefore, this patient was also excluded.

Table 2 provides what we believe is the fairest analysis of the fate of patients who had an AV at least 20 years previously. The attrition rate was similar to that seen in other studies. The need for aortic valve replacement along with the four patients who had a second AV produced a reoperation rate of 15 of 54 patients (28%). A surprising number of patients are either asymptomatic currently or were so at the time of last contact. The absence of symptoms does not always indicate the absence of significant residual problem; however, nine patients have been restudied and show only a mild (less than 40 mmHg) residual LV-Ao pressure difference. For these nine patients, the mean LV-Ao pressure difference was determined by echocardiography at the time indi-

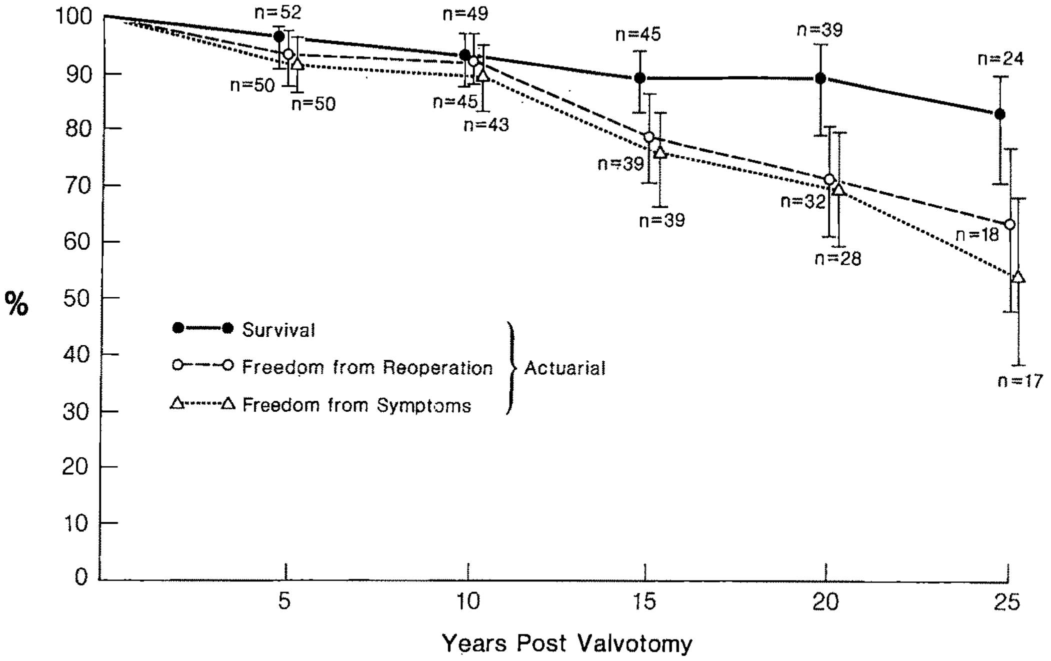

FIG. 2. Actuarial analysis of survival, freedom from reoperation, and freedom from symptoms for children undergoing aortic valvotomy. At each time point, the actuarial figure ± SD is given.

cated after AV: 20 years, 24 mmHg; 21 years, 35 mmHg; 24 years, 20 mmHg; 25 years, 23 mmHg; 25 years, 35 mmHg; 26 years, 35 mmHg; 26 years, 20 mmHg; 27 years, 35 mmHg; and 28 years, 25 mmHg. The remaining 25 asymptomatic patients who comprise 46% of the total group have not been restudied to determine whether or not they have a significant LV-Ao pressure difference. These data show that a significant subset exists that has only mild residual obstruction 20 years or more after AV. Additional patients may be members of this group but cannot be included because either no objective data are available or where, as in one case, the rare occurrence of palpitations prevents inclusion.

One of the important detrimental consequences of AV is the production of significant aortic regurgitation (AR). No preoperative AR was present in 77% of the children, and the effects of AV on AR in the presence or absence of preoperative AR are presented in Tables 3 and 4. For the entire series, 12 AVRs were done primarily for AR, whereas only seven were done primarily for aortic stenosis. Both lesions contributed to the need for valve replacement in two patients and the reason for valve replacement was unknown in an additional two patients for a total of 23 AVRs (23 of 155 patients, 15%).

TABLE 2. *Fate of Patients Undergoing Aortic Valvotomy more than 20 Years Ago*

	No. of Patients	Total
Late deaths		6 (11%)
0–19 years	4	
20–30 years	2	
Aortic valve replacement		11 (20%)
Asymptomatic currently	5	
Symptomatic currently	4	
Lost to follow-up	2	
Symptomatic currently		3 (6%)
DOE, after second AV	2	
Rare palpitations	1	
Asymptomatic currently		24 (44%)
Followed ≥20 years (24 patients)		
Studied ≥20 years, no residual gradient	9	
Studied <20 years, no residual gradient	3	
Studied <20 years, residual gradient	2	
Studied <20 years, residual gradient and second valvotomy, no restudy	2	
No study	8	
Asymptomatic at last contact		10 (19%)
Studied <20 years, no residual gradient	6	
Studied <20 years, residual gradient	1	
No study	3	
Total number of patients		54 (100%)

Discussion

Aortic valvotomy is widely accepted as the initial operative treatment of children with significant congenital aortic stenosis. Our data confirm that AV is effective initially in relieving the obstruction but the degree of valvar deformity encountered at operation is often dismaying. The reported relatively prompt reappearance of significant obstruction with return of symptoms and the need for a second operation confirms the palliative nature of AV.[1-5] Because the valve deformity is not corrected and only the obstruction is relieved to varying degrees, it is reasonable to conclude that AV at best delays valve replacement. The most pessimistic recent prediction has been that all patients will require reoperation within 20 years.[6]

Previous reports, however, have almost exclusively studied patients who have again become symptomatic and would be expected to have significant aortic valve problems. This study represents the first attempted follow-up of all patients, whether symptomatic or asymptomatic after AV. Analysis of this group of patients has allowed several significant conclusions to be drawn.

The first finding was that the operative technique of valvotomy has changed little, if any, over 30 years, whereas survival continues to improve. There were several early deaths, however, due to technical difficulties with cardiopulmonary bypass as would be expected with these pioneering efforts. The results have long been satisfactory, in terms of operative risk, for the group operated on at 1 year of age or older. No early deaths have occurred since 1965 as has been found in other series.[3] Results have also greatly improved in the infant group (15 days–1 year) and there has been no deaths over the past 10 years.

It is universally recognized, however, that the newborn group has had significant operative mortality.[3] The first report of a high survival rate in infants up to 3 months of age at operation appeared recently.[11] Our results also have shown a striking improvement. In the absence of severe accompanying abnormalities of the left ventricle, survival rates of 90% are to be expected even when the operation is done within the first 2 weeks of life. We have had six survivors 1–2 days of age at AV; therefore, very young age and grave condition are not the dominant risk factors. By retrospective analysis, we found the presence of HLV and significant EFE are the major determinants of failure.

Infants over 15 days of age are typically in congestive failure, but do not require pressor and ventilator support in preparation for AV. Nevertheless, the valve abnormality is severe and, as a reflection, the reoperation rate is over five times that of children. The actual reoperation rate for newborns and infants may be even higher because the follow-up period is significantly shorter than for children. There also has not been sufficient length of follow-up to determine if the long-term outlook for the newborn and infant groups differs.

It is the group operated on at 1 year of age or older, however, that has provided the most detailed and surprising long-term information. Our series, particularly the group of patients 20–30 years after AV, not only extends the period of AV follow-up by almost 10 years but, more importantly, contains pressure data on asymptomatic patients (Table 2).

As with other series, we also found a large group of patients with significant residual problems. Eight of the 12 late deaths were clearly related to aortic valve disease, and 28% of patients already have required a second operation. Follow-up of 25–30 years was available for only 18 patients, and it is anticipated that additional reoperations will be necessary as more patients live 30 years after the initial AV. Although a large number of patients have had late problems, the percentage is much less than some predictions.[6] Most series have shown a reoperation rate of 16–41% with a mean follow-up of 7–17 years.[1] Our series shows a similar reoperation rate with a longer follow-up.

TABLE 3. *Appearance of Valvar Regurgitation after Aortic Valvotomy*

	No. of Patients
No preoperative regurgitation	101
Postoperative regurgitation	
1+	13
2+	16
3+	7
4+	4
Total	40 (40%)
Valve replacement required	7 (7%)

On the other hand, our data also reveal a significant percentage of patients who show no discernible return of obstruction with objective follow-up of 5–28 years (Fig. 1 and Table 2). To more accurately assess the course of children after AV, we examined in detail the patients furthest from AV. We attempted to follow up and restudy all surviving patients who had AV 20 or more years ago (Table 2). Although not all patients have been restudied, a large percentage (63%) are currently asymptomatic or were at last contact. For nine patients (17%), recent study has revealed only mild aortic valvar obstruction. An additional nine patients (17%) are asymptomatic and had only mild obstruction at the time of last study. Consequently, a significant proportion of these patients have evidence of relief of obstruction more than 20 years after AV.

A more accurate and extended natural history of AV is provided by this report, but, of course, complete an-

TABLE 4. *Effect of Aortic Valvotomy on Preoperative Valvar Regurgitation*

	No. of Patients
Regurgitation present before operation	31
Trace	7 (23%)
1+	13 (42%)
2+	11 (35%)
Regurgitation after operation	
Worsened	14 (45%)
Unchanged	8 (26%)
Resolved	4 (13%)
No data	5 (16%)
Valve replacement required	5 (16%)

swers await life-long follow-up. It is possible that even the most favorable results will also fail with time because of calcification and other mechanisms of increasing valve damage. Nevertheless, this study demonstrated for the first time that a significant subset of patients receive long-term (greater than 20 years) relief of aortic valvar obstruction. Rather than a continuously progressive and relatively rapid reobstruction, this subset of patients enjoys extended benefit.

In apposition to the favorable group, there was significant attrition to late deaths (11%), a high reoperation rate (28%), and reappearance of symptoms (6%). For these patients, progression of valve dysfunction has been more rapid. One of the important consequences of AV is the production of significant AR. Precise analysis of the role of AV is difficult because our data also suggest that the preoperative incidence of AR increases with age. No discernible preoperative AR was present in patients under 1 year of age and an increasing incidence was observed the older the patient at the initial AV. In addition, when AR is assessed after operation by echocardiographic techniques, the severity may be overestimated. Nevertheless, 12 patients required valve replacement for AR.

We have found that more children require late aortic valve replacement for aortic regurgitation than for the recurrence of obstruction. Other studies have found the reverse to be true.[2,5,6] Although our incidence of valve replacement for regurgitation is not higher than other published results, replacement for recurrent obstruction appears to be less frequent. A possible explanation for the difference in the incidence of valve replacement for recurrent obstruction might be in the operative technique itself. Some authors recommend ending the valvotomy before the annulus and state that residual obstruction is preferable to the production of significant regurgitation.[3,4] In most of the patients in this series, valvotomy was carried to the annulus itself to provide maximum relief of obstruction. Our reoperation data would suggest that somewhat better relief of obstruction was achieved at no increased risk of significant aortic regurgitation. Because of the small numbers involved, these data are not conclusive. At the other end of the spectrum, Ankeny et al. have advocated creating a tricuspid valve whenever possible without an apparent increase in AR.[2] Other authors have recommended against this practice in all but the most favorable circumstances.[12] These divergent views are difficult to reconcile but, at the least, our data suggest that as complete relief of stenosis as is possible by creating a bicuspid valve does not result in a significant increase in AR.

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DISCUSSION

DR. HARVEY W. BENDER, JR. (Nashville, Tennessee): I would like to congratulate Dr. Foker on a nice presentation and to thank him and his coauthors for bringing this important long-term data to our attention.

We are currently looking at our experience with critical aortic stenosis in the newborn and would certainly agree with the comments made in the presentation today, in that this is a high-risk group and in our institution nonsurvival was clearly associated with pulmonary hypertension, small left ventricles, the presence of a patent ductus arteriosis at the time of presentation and in younger age at presentation.

With regard to long-term follow-up data, from your reported high incidence of reoperation in the children operated on less than 1 year of age, I would assume that reoperation in those individuals was related to aortic stenosis and that in this particular group of patients a number of the valves are quite dysplastic at the time of initial operation and a high, incidence of restenosis could be anticipated.

From data mentioned in the presentation and that published in the abstract, the fact that aortic regurgitation either increased or appeared as a new finding in approximately 40% of patients after operation would suggest that, the cut at the time of valvotomy was at least in some patients in areas where there was no commissural support. The fact that these individuals then went on to have a relatively low incidence of reoperation over the next three decades would suggest that mild to moderate aortic regurgitation is indeed a well-tolerated lesion.

This then raises the possibility that percutaneous balloon valvuloplasty may have a role in young children as their initial intervention.

DR. GEORGE A. TRUSLER (Toronto, Ontario, Canada): I congratulate the authors on their fine presentation and superb results. Although I realize that the main thrust of the paper has to do with the long-term results of aortic valvotomies in children over 1 month or at least over 1 year of age, I would like to ask the authors about the neonatal group which gives us most trouble. We admit that some infants have a hypoplastic left ventricle and EFE and are definitely inoperable, but there are other children where the left ventricle is borderline in size.

We found that the size of the aortic valve ring was helpful in deciding the adequacy of the left ventricle. We have not had any survivors who have a ring less than 5.5–6 mm in diameter relative to their size. I wonder if the authors would comment on how they judge whether the left ventricle is too small or an aortic valve ring is too small, and do they have any comment on the use of the valve ring size as an indicator?

Finally, is there a place for transventricular valvotomy when the size of the left ventricle and the valve ring is critical?

DR. JOHN E. FOKER (Closing discussion): I would like to thank the discussants for their kind remarks and their willingness to discuss this paper at this late hour.

It is clear that every one has far and away the most difficult time with the newborn group. What we have done is looked back to see what have been the determinants of survival in a retrospective analysis. Despite their critical condition at presentation, survival seems to be governed by whether or not the left ventricle has potential for adequate function. We need more data on what determines if a left ventricle will be inadequate. I realize that it remains a bit subjective, but a hypoplastic left ventricle in the view of our cardiologists is not only small but also consists of a spherical shape, with a longitudinal dimension no greater than the transverse dimension. In terms of size, a transverse dimension of less than 12 mm qualifies as a hypoplastic left ventricle.

Dr. Trusler, we have not used the absolute size of the aortic annulus as a means of determining whether these children will do well or not. I believe that that certainly is an excellent suggestion, and as Dr. Bender stated and all of us know, it is these very young patients who have very severe stenosis and in whom the relief will be incomplete. The annulus will not grow well and they will require repeat operation much sooner.

We have looked carefully at the question of aortic regurgitation in these patients. In most cases we do a more complete valvotomy than often reported in the literature and carry the incision to the annulus as opposed to stopping short of it. It does not appear that our postvalvotomy regurgitation rate is significantly greater than that reported in the literature. Although more than half of the valves that came to replacement in our series were done primarily for regurgitation, the incidence does not appear higher than reported. Recently, regurgitation has been assessed mainly by echocardiography and some degree of regurgitation was found in about 40% of postvalvotomy patients. As you know, echo can spot small degrees of regurgitation and currently it tends to be overcalled. A longer time and more data will be needed until we can judge the significance of the echo findings.

Valvotomy in the newborn is sometimes difficult, as is determining where the commissures are, particularly when they have a unicommissural valve. Nevertheless, we attempt to locate the major area of fusion and divide it and I believe this will provide the best relief with the least regurgitation. With its drawbacks, I believe that valvotomy is still preferable to balloon dilation. Balloon dilation, which was pioneered at Minnesota by Jim Lock, who is now at Boston, may produce a greater frequency of significant regurgitation. I am skeptical that it will prove to be as satisfactory for initial treatment as an operation.

The role of balloon dilation, however, may be in place of a second valvotomy because the commissural incision already has been made. Balloon dilation would not be as likely to tear out into the cusp itself and may be as good as a repeat valvotomy.

Finally, we have had no experience that I am aware of with transventricular valvotomy.

Ileal Pouch–Anal Anastomosis for Chronic Ulcerative Colitis

Long-term Results

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BRUCE G. WOLFF, M.D., and DUANE M. ILSTRUP

The aim of this study was to determine the long-term outcome among 390 patients with ulcerative colitis who underwent ileal J pouch–anal anastomosis and whether patient or operative factors influenced results. The combined operative morbidity rate for the pouch–anal anastomosis and the subsequent closure of the temporary ileostomy was 29% (bowel obstruction, 22%; pelvic sepsis, 5%), with one death due to pulmonary embolus. The probability of a successful outcome at 5 years was 94%. Of the 24 patients who failed (6% of total), 18 did so within 1 year (4%), three during year 2 (1%), three during year 3 (1%), and none thereafter. Stool frequency (7 stools/24 h), the occurrence of pouchitis (14%), and satisfactory daytime continence (94% of patients) remained stable over 4 years after operation, whereas nocturnal fecal spotting decreased (51% of patients to 20%). Women had more spotting than men, whereas patients over 50 years old had more stools per day than those 50 years or younger. In conclusion, ileal pouch–anal anastomosis achieved a reasonable stool frequency and satisfactory continence in patients with ulcerative colitis over the long-term. These results support the ileal pouch–anal anastomosis as a safe, satisfactory alternative to permanent ileostomy.

From the Departments of Surgery and Medical Statistics and Epidemiology, Mayo Medical School, Rochester, Minnesota

SINCE THE REPORT by Martin and colleagues in 1977,[1] ileoanal anastomosis and, more recently, ileal pouch–anal anastomosis has become a popular surgical alternative among some surgeons for patients with chronic ulcerative colitis. The reasons for this popularity are severalfold. The disease is "cured" by the colectomy, proximal proctectomy, and distal endorectal mucosal resection. Reasonable enteric continence is maintained because the anal sphincters are preserved. The reservoir capacity of the distal bowel is restored by incorporating an ileal pouch. The necessity for ileostomy is eliminated.

The impact of such a curative yet continence-preserving operation could be profound; appropriately timed surgical intervention might become more acceptable to patients and their physicians and, in turn, earlier referral for operation, when conditions for a successful outcome are optimal, would be assured. The potential attractions of the ileal pouch–anal anastomosis, however, must be balanced by the fact that the operation is relatively new and the long-term results unknown.

Since our survey of the literature 5 years ago,[2] which detailed the clinical results of 25 series of ileoanal patients during the preceding 48 years, 66 additional reports have been published. None of these past studies, however, has documented the clinical and functional results of the operation in a large group of patients with a single disease, operated on in a single institution, using the same operative technique, with a follow-up over the longer term. Therefore, our aims were to investigate the clinical results of patients operated on only for ulcerative colitis, all of whom had an ileal "J" pouch–anal anastomosis performed at the two Mayo-affiliated hospitals. We also sought to determine whether the functional results improved, deteriorated, or remained stable over time, and whether operative or patient factors influenced results.

Patients and Methods

Between January 1981, and January 1986, 522 patients underwent ileal pouch–anal anastomosis for either ulcerative colitis or familial polyposis coli at Mayo. Four hundred thirty-two patients had the operation per-

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formed for ulcerative colitis using the two limb "J" shaped ileal reservoir design similar to that described by Utsunomiya and associates.[3] Three hundred ninety patients have been followed for 6 months to 5 years (mean: 2.3 years) and form the basis of this report.

One half of the patients were men. The mean (±SD) age of the group was 31 ± 9 years. The patients passed a mean (±SD) of 9 ± 5 stools/day before operation. Moreover, 15% of patients had intermittent (2 times/week or less) loss of small amounts of stool (spotting) and 5% were more frequently and grossly incontinent before the operation. One half of the patients (49%) complained of sexual difficulties; 21% stated they did not engage in any sexual activity because of their disease and an additional 28% reported their activity was reduced abnormally. Symptoms of urinary urgency, frequency, and difficulty with the urinary stream were reported by 5% of the patients.

Abdominal colectomy, proximal proctectomy, resection of the distal rectal mucosa, ileal J pouch–anal anastomosis, and construction of a temporary diverting ileostomy comprised the first stage of the operation. The rectal mucosal resection was conducted from below, beginning at the dentate line and including the columns of Morgagni. The dissection proceeded proximally to 1–2 cm above the levator ani muscle complex; the resulting cuff of remaining rectal tunica muscularis was therefore 3–5 cm in length.

The "J" pouch was constructed from two 15–20-cm limbs of terminal ileum that were either stapled[4] or sutured together. The pouch was pulled through the short rectal muscular cuff and anchored circumferentially to the internal sphincter and puborectal muscle. Sutures were then placed such that the sensitive anoderm,[5] which was left *in situ,* was anastomosed to the mucosa of the pouch at the level of the dentate line (Fig. 1).

Three hundred sixty-three patients (92%) had a diverting ileostomy (loop, 95%; Brooke, 5%) established concomitantly, whereas 27 patients did not. The temporary stoma was placed 25–30 cm proximal to the pouch. After tests were later performed to determine the integrity of the anastomosis and the function of the anal sphincters, the ileostomy was closed at a second operation. The stoma was resected and an end-to-end anastomosis constructed in 38%, whereas the remaining patients had simple closure. The midline incision was reentered in 17% of the patients because adhesions prevented the safe closure of the ileostomy through a peristomal incision. The mean (±SD) interval from ileal pouch–anal anastomosis to ileostomy closure was 95 ± 60 days (median: 76 days).

A data file was established for each patient that contained preoperative, postoperative, and follow-up information. Preoperative data included stool frequency, history of incontinence, and whether sexual or urinary problems were present. Postoperative data included mortality, morbidity (pelvic infection, intestinal obstruction, wound infection, and others), use of medication, degree of continence, and stool frequency at dismissal after closure of ileostomy. Follow-up data included stool frequency, degree of continence, stool consistency, whether gas could be discriminated from stool; use of medication; sexual and urinary problems; occurrence of pouchitis; and failure of the operation. Follow-up of all patients was initiated at 6 months after closure of the ileostomy and conducted yearly thereafter by a data clerk. At no time did a surgeon enter data into the file or conduct follow-up surveys.

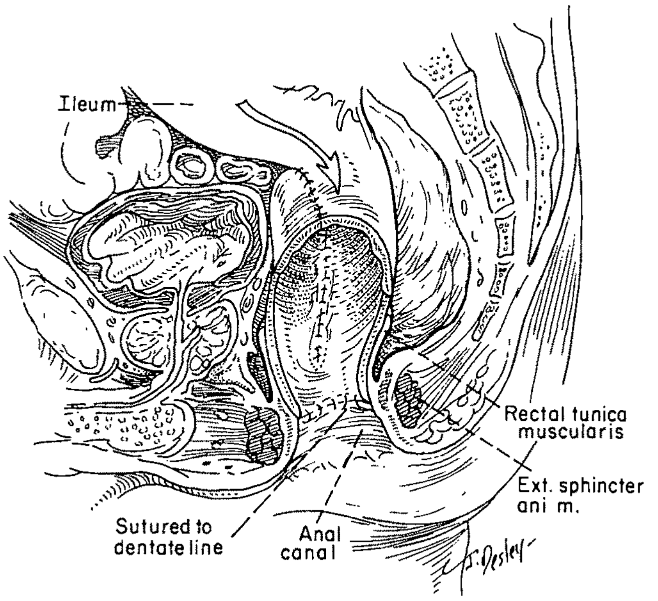

FIG. 1. Diagram of completed ileal "J" pouch anastomosed to the internal sphincter and the anoderm.

Although difficult to define precisely, incontinence during the day and night was recorded as none, spotting (1–2 episodes/week), or frequent and gross (more than 2 episodes/week). Pouchitis was identified as a syndrome manifest as frequent watery, often bloody stools, urgency, incontinence, abdominal cramping, malaise, and fever. An episode of pouchitis was considered to have occurred if these symptoms were present for 2 or more days and was promptly relieved (within 48 hours) by the administration of metronidazole, 250 mg q.i.d. Failure of the operation was defined as establishment of a permanent ileostomy, with or without excision of the pelvic pouch.

Analysis of Data

Proportions were compared in two or more groups with chi-square tests or, where appropriate, with Fisher's

TABLE 1. *Postoperative Morbidity after Ileal Pouch–Anal Anastomosis and after Closure of the Ileostomy in 390 Patients*

Complication	% of Patients with Complication
After ileal pouch–anal anastomosis	
Small bowel obstruction	13
Transient	8
Required reoperation	5
Pelvic sepsis	5
Antibiotics alone	3
Required reoperation	3
Wound infection	3
Urinary retention	7
Transient	5
Required catheterization	2
After closure of ileostomy	
Small bowel obstruction	9
Transient	4
Required reoperation	5
Anastomotic leakage	2

exact test. Changes over time of an event within individuals were analyzed with the sign test or with signed-rank tests for ordinal variables. Ordinal variables were compared in two or more groups with rank-sum procedures. The probability of the occurrence of an event in a fixed period was modeled multivariately with the logistic regression model. Comparisons of continuous variables were made with student's t-test or, where appropriate, with rank-sum tests. Survivorship free of pouch excision was estimated by the Kaplan-Meier method. Comparisons of survivorship curves were made with log-rank tests. Survivorship was modeled multivariately with Cox's proportional hazards model.

Results

Clinical Outcome

Early. One of the 390 patients (0.2%) had a massive pulmonary embolus and died 2 weeks after dismissal from the initial operation. Overall, 29% of patients had a postoperative complication after either the initial or the second operation (Table 1). After the first operation, the most frequent complication was small bowel obstruction, which occurred in 51 patients (13%). Twenty of the 51 patients (5% overall) required reoperation, primarily to lyse adhesions, whereas the remainder resolved spontaneously. Pelvic sepsis occurred in 5% of the patients. Pelvic sepsis was manifest clinically as fever, leukocytosis, and localized abdominal tenderness and, on computed tomographic (CT) scan, either as a phlegmon or an obvious abscess. One third of the patients were treated successfully by antibiotic therapy alone, whereas the other two thirds required operative drainage. Abdominal wound infections occurred in 3% of patients. Urinary retention was a transient problem in 7% of patients, but required intermittent catheterization in less than 2%.

After closure of the ileostomy, 9% of patients had a small bowel obstruction for which operative correction was required in 5%. Anastomotic leakage at the site of the closure occurred in 2% and usually required re-establishment of the ileal stoma. All such patients, however, had re-establishment of intestinal continuity subsequently.

Late. The principle late complications were anastomotic stricture and pouchitis. Many patients had a filmy, web-like stricture at the anastomosis at the time of ileostomy closure; these were easily dilated and did not recur. Five per cent of the patients, however, had persistent strictures that required dilation intermittently. Pouchitis occurred at variable times throughout the postoperative period in 14% of patients; the initial onset of symptoms varied from 1 to 2 months after closure of the ileostomy to as long as 5 years after closure. The mean (±SD) interval from operation to occurrence of pouchitis was 16 ± 14 months. Four per cent of patients had multiple episodes. Administration of metronidazole (250 mg q.i.d.) nearly always resulted in a prompt response. Several patients, however, required low-dose metronidazol therapy (250 mg q.d.) continuously to prevent recurrence of the syndrome.

Sexual dysfunction occurred in 11% of the men and 12% of the women overall. Three men (1.5%) were impotent, seven (4%) complained of retrograde ejaculation, and the remainder reported lack of motivation or fatigue as the causes of sexual inactivity. Dyspareunia was the principle sexual complaint in women and occurred in 7%, while 3% of women stated that the fear of leakage of stool inhibited sexual relations.

Functional Outcome

Early. At the time of dismissal from the hospital after closure of the ileostomy, the patients had a mean (±SD) stool frequency of 6 ± 2 stools/day with 1 ± 1 stools at night. Sixty per cent of the patients were always continent, 36% had occasional fecal spotting, and 4% had episodes of gross incontinence. Fifty-five per cent of the patients were placed on antidiarrheal medication, and 56% were dismissed using stool bulking agents.

Late. Nearly all patients had a favorable outcome over the long-term (Fig. 2). Only 24 of the 389 patients (6%) had a permanent ileostomy established and, therefore, failed the operation. The causes of failure, alone or in combination, were recurrent pouchitis, multiple stools, gross nighttime fecal incontinence, and granulomatous ileitis. Of the 24 patients who failed, 18 failed within 1 year (4% of the total patients operated), three

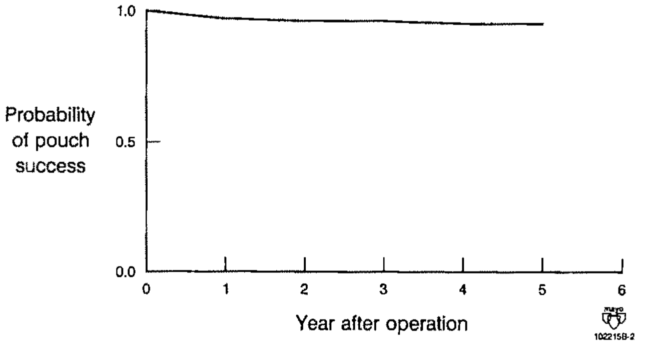

FIG. 2. The probability of successful outcome with functioning pouch against year after operation. No patient failed after 3 years.

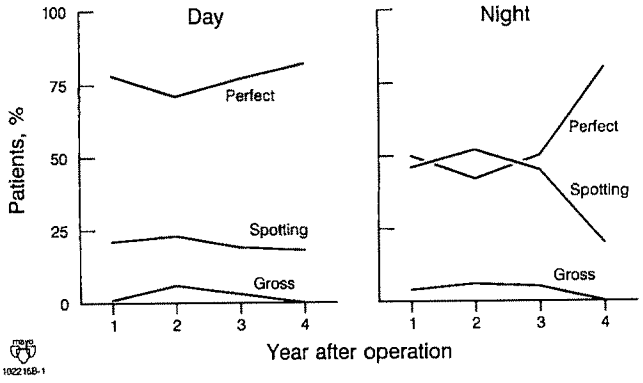

FIG. 3. Daytime and nighttime continence after ileal pouch–anal operation against the years after operation. Perfect = no fecal leakage. Spotting = fecal spotting of underclothes, 3 cm or less in diameter, two times or less per week. Gross = gross fecal incontinence more than two times per week. Data points are connected for illustrative purposes.

during the second year (1%), three during the third year (1%), and none thereafter.

All patients could evacuate the ileal pouch spontaneously; none required intubation. Table 2 and Figure 3 detail the stool frequency, pattern of continence, ability to discriminate gas from stool, and use of medication from 6 months to 5 years after ileal pouch–anal anastomosis. The daytime and nighttime stool frequency as well as the pattern of daytime continence did not change as the patients were followed after operation. In contrast, the incidence of nocturnal incontinence and dependency on medications declined. Moreover, the ability to discriminate gas from stool appeared to improve. By a mean of 2.3 years after operation, 33% of the patients had solid stools, 58% had semiformed stools, and 8% had liquid stools. Whereas the mean ± SD stool frequency was 9 ± 5 stools/day before operation, it had decreased to 6 ± 2 stools/day after operation ($p < 0.001$).

To determine whether clinical and functional results had improved as experience with the operation increased, results in the first 195 patients were compared with those of the second 195 patients (Table 3). Although the overall rate of complications did not differ between the groups, the incidence of some complications, such as the need to reoperate for obstruction after the initial operation and the rate of small bowel obstruction after the second operation, were less among the latter 195 patients. Moreover, urinary problems occurred with less frequency in the more recent patients. Functionally, however, the stool frequency and degree of continence were no different between groups at 1 year. Therefore, although some aspects of perioperative morbidity appeared to improve, the impact of that improvement on later function was nil.

A criticism of these data is that they are based on a comparison between different patient populations, and that factors other than time might have produced these differences. However, a subset of the patients ($N = 93$) had follow-up data available both at 1 year after operation and again at 3 years after operation (Table 4). The findings in this group were nearly identical to those of the larger group. Stool frequency and daytime continence remained stable, whereas nighttime incontinence clearly improved ($p < 0.05$).

Determinants of Outcome

Stool frequency. Older patients had more stools during the day than did younger patients at a mean of 2.3

TABLE 2. *Functional Results of Ileal Pouch-Anal Anastomosis from 6 Months to 5 Years After Operation in 389 Patients*

	Follow-up					
Parameter	6 mo	1 yr	2 yr	3 yr	4 yr	5 yr
No. of stools (mean ± SD)						
Day	5 ± 2	5 ± 3	6 ± 3	6 ± 2	6 ± 3	6 ± 2
Night	1 ± 1	1 ± 1	2 ± 2	2 ± 1	1 ± 1	2 ± 1
Able to discriminate gas from stool (% of patients)	69	77	73	84	77	86
Lomotil (% of patients)	26	19	17	25	6	4
Metamucil (% of patients)	43	36	40	38	30	27

TABLE 3. *Comparison of Clinical and Functional Results of Ileal Pouch–Anal Anastomosis Between the First 195 Patients Operated On and the Second 195 Patients*

	Group of Patients		
	First	Second	p
Mean age (years)	31	31	NS
Sex (men:women)	1:1	1:1	NS
Overall complications (% of patients)	31	26	NS
Reoperation for obstruction after IPAA (% of patients)	10	4	<0.02
Obstruction after ileostomy closure (% of patients)	13	3	<0.01
Urinary retention (% of patients)	11	3	<0.04
Mean stool frequency ± SD at 1 year			
Day	6 ± 2	6 ± 3	NS
Night	1 ± 1	1 ± 1	NS
Never incontinent at 1 year (% of patients)			
Day	75	80	NS
Night	47	48	NS

years after operation (≤50 years, 6 ± 3 stools/day; >50 years, 8 ± 4 stools/day; $p = 0.05$). Older patients did not, however, have more stools at night. Stool frequency was not different between men and women. Postoperative small bowel obstruction did not predispose to increased stool frequencies. Not surprisingly, we found that the greater the number of stools, the more frequently patients were incontinent (Table 5). Whether patients had pouchitits or ultimately failed the operation could not be predicted by the preoperative or immediate postoperative stool frequency.

Incontinence. The age of the patients did not correlate with the ability to achieve continence after ileal pouch–anal anastomosis. Patients who had postoperative bowel obstruction were no more likely to be incontinent at follow-up than those who did not. Women, however, had more fecal spotting than did men both during the day and night (day: women, 33%, *vs.* men, 14%, $p < 0.001$; night: women, 56%, *vs.* men, 44%, $p < 0.02$). Although patients who were incontinent before operation were more often incontinent early after closure of the ileostomy ($p < 0.001$), such early incontinence did not influence the ability to achieve continence later.

TABLE 4. *Comparison of Functional Results in the Same 93 Patients 1 Year and 3 Years after Operation*

	Period After Operation	
Parameter	1 Year	3 Years
Stool frequency (mean ± SD)		
Day	6 ± 2	6 ± 3
Night	1 ± 1	1 ± 1
Incontinent, spotting and gross (% of patients)		
Day	11	9
Night	30	13*
Lomotil use (% of patients)	30	18

* $p < 0.05$ compared with 1 year value.

TABLE 5. *Relationship of Postoperative Incontinence to Later Stool Frequency (N = 389 Patients)*

	Mean ± SD No. of Stools at Follow-up (mean: 2.3 years)	
Postoperative Incontinence	Day	Night
At follow-up mean: 2.3 years		
No	5.6 ± 2.3	1.2 ± 1.0
Yes, spotting	7.5 ± 4.5	1.9 ± 1.3
Yes, gross	10.2 ± 3.9*	3.4 ± 3.0*

* $p < 0.001$ rank-sum test.

Pelvic sepsis. The development of pelvic sepsis was not correlated with age or gender of the patients. Importantly, pelvic sepsis did not appear to affect the degree of early or late continence achieved by the patients nor the early or late stool frequency. Furthermore, patients who had pelvic sepsis were no more likely to fail the operation than those who did not. However, if pelvic sepsis occurred, closure of the ileostomy was delayed appreciably (no sepsis, mean interval between ileal pouch–anal anastomosis and closure = 94 days, *vs.* sepsis = 141 days, $p < 0.002$).

Pouchitis. The occurrence of pouchitis did not correlate with the age or sex of the patients. Patients in whom pouchitis developed were no more likely to have had pelvic sepsis or other postoperative complications than those who did not. Moreover, sexual and urinary problems did not occur with any higher frequency in patients who had episodes of pouchitis.

Sexual and urinary dysfunction. Older patients did not have more sexual problems before operation than younger patients, nor did men have more sexual difficulties before operation than women. However, older patients had more sexual dysfunction after operation than did younger patients (no problem, mean age: 30 years *vs.* problem, mean age: 36 years; $p < 0.001$). In addition, patients with sexual problems tended to have a slightly higher stool frequency than those who did not and were more likely to be incontinent during the day and night. The incidence of both sexual and urinary dysfunction did not differ between men and women. Finally, pelvic sepsis did not predispose patients to later sexual or urinary problems.

Multiple Regression Analysis

Using a Cox proportional hazards model, multivariate analysis of age, occurrence of pelvic sepsis, incontinence (before operation or at dismissal), and preoperative and dismissal stool frequency showed no significant effect on either ultimate failure of the operation, late stool frequency, or development of pouchitis. However, the incidence of incontinence at follow-up was significantly affected by the preoperative stool frequency; the more stools before ileal pouch–anal anastomosis, the more likely patients were to be incontinent after operation (beta weight: 0.13; $p < 0.03$).

Discussion

Patients with chronic ulcerative colitis are "cured" of their colitis by proctocolectomy. Sometimes lesser operations, such as ileorectostomy, are performed in selected patients with good results. Complete removal of *all* diseased colonic mucosa, however, is the ideal central goal of surgery for ulcerative colitis. The ileal pouch–anal anastomosis operation accomplishes this goal, retains the usual transanal anatomic pathway for defecation, and maintains reasonable continence. However, because the operation is new and unproven, its widespread acceptance as a surgical alternative awaits documentation that it is safe, has acceptable morbidity, achieves its promised clinical and functional goals in most patients, and performs predictably over time.

This study found that ileal pouch–anal anastomosis can be performed safely, but that morbidity was high; 29% of patients had a postoperative complication. The major complications were obstruction of the small intestine, pelvic infection, and pouchitis. Overall, 22% of patients had a small bowel obstruction in the immediate postoperative period. Five per cent of these patients required reoperation after the initial procedure, and an additional 5% after closure of the ileostomy. This 10% reoperation rate, although greater than desirable, is similar to the 7–13% incidence of reoperation for obstruction reported after proctocolectomy and permanent ileostomy[6–9] and the 15–20% incidence reported after ileorectostomy.[10,11] Construction of a loop ileostomy might predispose to obstructive complications,[12] such as torsion of the afferent limb about the mesentery of the stoma. We agree with others,[13] however, that episodes of obstruction were related more to postoperative adhesions than to the type of ileostomy used. Our experience with other types of stomas, or with no stoma at all, has shown no clear advantages over the loop configuration. Therefore, we continue to use this stoma in most patients.

Pelvic infections occurred in 5% of the patients. Although Becker and Raymond[13] reported no pelvic sepsis in 100 patients who had ileal pouch–anal anastomosis, Williams and Johnston, summarizing the results of nine series, found the mean rate of pelvic infection to be 18%.[14] Indeed, the rate of pelvic sepsis reported previously from our institution was 11%.[15] The decrease in the rate of pelvic sepsis in the current report is substantial and may reflect improved techniques for excising the rectal mucosa, use of a shorter muscular cuff, and more effective drainage of the pelvic space.[4] We could not find a correlation, however, between the occurrence of pelvic sepsis and impaired function, the development of late complications, or failure of the operation. Nevertheless, the sequelae of pelvic infections can be devastating; pelvic fibrosis, anastomotic stricture with overflow incontinence, persistent sinuses, and fistulae can lead to incapacitating dysfunction and ultimate failure of the operation.

The most vexing medical problem in our patients continued to be pouchitis. This syndrome occurred with no predictability and at various times after operation. The cause of pouchitis is obscure, but resembles the syndrome seen in patients with continent ileostomies. In these patients, bacterial overgrowth in the pouch[16] and in the proximal small intestine[17] has been described. O'Connell et al.[18] documented similar bacterial overgrowth in patients after ileal pouch–anal anastomosis. However, they found no correlation between such overgrowth and a poor result. Because such patients respond to metronidazole, pouchitis is likely caused either directly by bacteria, or by a mucosal response to the presence of bacteria within the pouch. Not all patients with crampy abdominal pain and watery diarrhea after ileal pouch–anal anastomosis, however, have pouchitis. In patients who do not respond rapidly to metronidazole, outflow obstruction from the pouch, secondary to narrowing at the anastomosis, may cause increased stool frequency and incontinence.

In terms of ultimate failure of the operation, the 6% failure rate reported here is similar to that reported by others.[12,14] Because the number of patients who failed was small and the reasons for failure so varied, no single factor was found to correlate significantly with excision of the pouch. It was reassuring, however, that most failures (75%) occurred early, during the first year, and that no patient had a delayed failure (>3 years).

In terms of the number of stools and the degree of continence achieved by the patients, the long-term functional results of ileal pouch–anal anastomosis were relatively stable. We reported earlier that stool frequency improved in the first 6–18 months after operation.[15] The current series shows that after this initial period, the mean daytime and nighttime stool frequency and the level of daytime continence vary little from 1 to 5 years after operation. That the stool frequency did not decline with time may be partially explained by our findings that stool frequency is directly related to the daily amount of stool output and indirectly related to the threshold volume and to the efficiency of pouch emptying.[19] Threshold volume is that volume of enteric content present in the pouch that triggers waves of high pressure. Such pressure waves are uncomfortable, herald the call to stool, and if large enough, may overwhelm the resting and squeeze pressures generated by the anal sphincters. The efficiency of evacuation can be measured using radiolabeled artificial stool and gamma camera imaging.[20]

Because most patients evacuate 50–60% of the threshold volume (which is approximately 45% of the maximum pouch capacity of approximately 320 mL)[19] and because the mean output of stool per day is between 400–800 mL, patients will naturally evacuate four to eight times per day. It follows, therefore, that stool frequency may be decreased by either decreasing the total output per day, increasing the efficiency of emptying, or increasing the threshold volume. Of these, the easiest to achieve would be to increase the threshold volume by increasing the maximum capacity. To this end, several workers have advocated a "W"-shaped pouch, which apparently provides a larger initial volume than that of the "J" design and consequently results in a lower stool frequency and improved continence.[21,22] It will be important, however, to determine if the advantages of such higher capacity are offset by more inefficient emptying of the pouch.

Although daytime continence remained stable after operation, encouragingly, the incidence of occasional fecal spotting at night decreased from 51% at 6 months to 20% at 4 years after operation and gross incontinence decreased from 4% to 0%. The incidence of both, however, rose slightly at 5 years. This finding might be caused by gender sampling bias; whereas the ratio of women to men was 1:1 at each interval from 6 months to 4 years, at 5 years it was 2:1. Overall, we found women had more daytime and nighttime incontinence than men at each follow-up interval, an observation that differs from our earlier report.[15] The reasons for this finding are unknown. However, women generally have more problems with fecal continence than men.[23] Thus, our results may merely reflect a gender predisposition to incontinence that persists after ileal pouch–anal anastomosis.

The single preoperative factor that was found by multivariate analysis to have influenced continence after ileal pouch–anal anastomosis was the preoperative stool frequency. Although no studies have documented the impact of severity of disease on the functional outcome of patients after ileal pouch–anal anastomosis, this aspect of our results suggests that the more decompensated the patient before operation, in terms of stool frequency, the more problems with continence after operation.

We confirmed our earlier report that serious sexual problems were relatively few after ileal pouch–anal anastomosis. However, we found that three men (1.5% of the total at risk) were impotent. After proctocolectomy and permanent ileostomy for inflammatory bowel disease, the rate of impotency ranges between 5% and 12%,[14] whereas after ileorectal anastomosis, no patients have been reported to be impotent. Our results, therefore, fall in between these extremes and are in keeping with the observation of others[12,14] that difficulty with erection after ileal pouch–anal anastomosis can occur. The 4% incidence of retrograde ejaculation is similar to that reported by others[13,14] and is probably caused by disruption of the pelvic sympathetics. Although this incidence is lower than the 9% reported earlier from our institution,[15] the problem remains troublesome.

The major functional disturbance in women continued to be painful intercourse (7%), the incidence of which, although unchanged from our previous report, continues to be substantially lower than the 53% reported after ileorectal anastomosis.[24] In addition, fear of leakage of stool inhibited sexual relations in an additional 3%; indeed, the higher the stool frequency and rate of incontinence, the more likely patients were to have sexual problems. Reassuringly, however, the potentially serious complication of pelvic infection did not appear to predispose patients to later sexual dysfunction.

In summary, ileal pouch–anal anastomosis is a safe operation but carries a significant risk of complications. If a complication such as pelvic sepsis or small bowel obstruction occurs, however, it does not appear to predispose the patient to unacceptable stool frequencies, more incontinence, or an increased chance of failure. The functional parameters of stool frequency and daytime continence, which improved early after operation,[15] reached a plateau by 2 years and remained stable thereafter. Nighttime incontinence and dependency on medications, however, continued to diminish.

Our data show that the best results with ileal pouch–anal anastomosis occur in young, male patients who are not compromised severely before the operation. There is no question, however, that the operation is not perfect, that it is complicated, that some patients are not candidates, that morbidity, particularly obstruction and pouchitis, remain troublesome, that incontinence, although improving with time, affects patients adversely, and that failures continue to occur. Balancing these problems are the observations that the great majority of patients with ileal pouch–anal anastomosis achieve satisfactory enteric continence, maintain willful defecation, retain essentially normal urinary and sexual function, and do not have a stoma. Although no operation can make a patient with chronic ulcerative colitis "normal," of the curative surgical procedures available today, that which comes closest to the norm is ileal pouch–anal anastomosis. Based on these long-term results, ileal pouch–anal anastomosis can be recommended to the majority of patients who require operation for chronic ulcerative colitis.

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DISCUSSION

DR. ARNOLD G. CORAN (Ann Arbor, Michigan): I would like to congratulate the authors on an excellent series, probably the largest series of endorectal pullthroughs reported thus far in the literature.

I would also like to thank them for asking me to discuss their paper. I do so with great humility since our experience at the University of Michigan is far less than theirs.

Since 1977, we have done 80 straight endorectal pullthroughs without a reservoir on patients with ulcerative colitis and familial polyposis who range in age from 4 to 48 years. Six of these patients were reconverted to a Brook ileostomy of which three were done because of dissatisfaction with stool frequency.

Daytime continence was achieved in all of these patients within 1 month after closing the temporary ileostomy and nocturnal incontinence occurred in the first year in six of these patients and then finally disappeared.

(Slide) The mean stool frequency in this group declined progressively over the first 3 years to 8 per 24 hours, which compares favorably with the six reported in the current series.

We have also analyzed the stool frequency by age groups above and below 18 years of age and above and below 30 years of age and could find no statistical difference. We also analyzed them by gender and again found no differences. This is consistent with our finding as you will see in the next slide (Slide) that the neorectum progressively dilates over this 3-year period, finally achieving what appears to be a normal rectal reservoir capacity 2–3 years after the endorectal pullthrough.

I would like to ask the authors three questions: how did they specifically obtain their follow-up data on stool frequency and continence? We found that frequent and close follow-up of our patients is necessary to determine what the actual frequency is. For example, we find sometimes that a stool frequency can vary by 100% if, in the case of a college student, they are getting ready for final exams, if there is marital strife, etc. I have seen patients with an average frequency of three stools a day increase their frequency to 10 or 12 under emotional stress.

Second, how exactly was the endorectal dissection done? Was any of it done from above or below or both ways, and in those cases, was the intact mucosal-submucosal tube removed so that they feel assured that all the potential disease has been removed?

Third, were there times when the "J" pouch could not be performed because of significant tension at the anastomosis?

I have occasionally had to do a "J" pouch because the tension at the anastomosis with a straight pullthrough was too great and *vice versa.* I am wondering that the authors did in the cases where there was too much tension.

Essentially, it appears that the results with the straight endorectal pullthrough in our much smaller series and the results with the ileal pouch anal anastomosis are similar in terms of continence, frequency, and complications. I do believe that the straight pullthrough is somewhat easier to do and takes less time. In general, the operation takes us about 3.5–4 hours and we seldom use blood.

Probably, as has been the experience with Hirschsprung's disease, the most important factor in the results of this operation is the experience of the surgeon.

DR. ERIC W. FONKALSRUD (Los Angeles, California): I would like to congratulate Drs. Pemberton, Kelly, and their colleagues at the Mayo Clinic for providing us with a very carefully performed detailed analysis of the long-term excellent results after the endorectal ileal pullthrough procedure with a "J" reservoir for ulcerative colitis excluding the polyposis patients.

Although the operative technique used by each of the five surgeons from their hospital was similar in this series with little variation during the 5-year period of study, the optimal technique for the pullthrough procedure for colitis may not as yet have been determined as was mentioned by Dr. Coran.

In a recent review of 1771 patients compiled from reports from 17 different hospitals using various types of reservoir, the failure rate was remarkably similar in this large group, with 7.2% failures when no reservoir was used, 5.6% with the "J", 6.4% with the "S", and 4.2% with the lateral reservoir. Nonetheless, the incidence of complications varied considerably, and the average follow-up was less than that reported today.

The authors report only slightly better results in the last 195 patients compared with the first 195 in their manuscript; a somewhat different observation than that for most other hospitals where there has been a steep learning curve with improvement in results as modifications in technique have been made. In our experience with 165 patients at the UCLA Medical Center in which the lateral ileal reservoir was used in 141, 6 patients (4%) were failures and returned to permanent ileostomy and 14 (10%) were given a temporary ileostomy, eight of which have subsequently been closed. Over 60% of the reoperations performed in our series were performed in the first 50 patients. Only two of the last 100 patients were failures and the incidence of reoperation was greatly reduced.

The authors indicate essentially stable results after the first year as determined by return to the ileostomy, stool frequency, and daytime continence, but note an increase in pouchitis at 16–18 months after operation. In our experience, pouchitis also was noted in over 35% of our early cases and was heralded by an increase in stool frequency, gas, and diarrhea more than 1 year after operation. In all but one of these patients the reservoir had elongated or enlarged causing reservoir stasis and increase in bacterial growth, poor emptying, and a decrease in absorption of bile acids. Reoperation to shorten the reservoir to a length of 12–15 cm and repair of any outlet obstruction has relieved the symptoms in almost all patients. We now rarely construct a reservoir longer than 12–15 cm at the initial operation. It appears that the initial results are good with a big reservoir but become worse as the reservoir enlarges with time.

My first question to the author is: have they observed a direct relationship between the size of their reservoir and the development of pouchitis in later years since some of their reservoirs were 20 cm or longer? It would appear that the more complex pouches such as the "S" and more recently the "W" may be even more prone to late distention with stasis and may also be technically difficult to revise in subsequent years.

The authors report a somewhat higher incidence of sexual and bladder dysfunction than that reported in many other series. The second question is: do you believe that removing the rectal muscle down to within 3–4 cm of the dentate line is necessary since a slightly longer muscle cuff in males may be a bit safer and not alter the long-term results?

The authors have used the same technical operation for all patients with colitis. It appears that obese patients, those with severe anal sphincter spasm, and children, will do better with a short reservoir of 10–12 cm in length or no reservoir at all as Dr. Coran just mentioned and as was used in 15 of our patients during the past 2 years. Question number three: from your large clinical experience, have you considered tailoring the operation to the anatomic and physiologic differences between your patients? With this in mind should we not refer to this operation as the endorectal ileal pullthrough rather than the pouch procedure?

Again I compliment the authors on their pioneering work in this field and for providing us with an excellent detailed analysis of their long-term results with a very large series of patients.

DR. MALCOLM C. VEIDENHEIMER (Burlington, Massachusetts): It was with great pleasure that I received the manuscript from the Mayo Clinic. The Mayo experience so closely parallels our own that I have little to add in the way of criticism or critique for this paper.

We have now performed this operation for more than 200 patients. We have 23 who had an "S" pouch, and the surgeon in our group who used the "S" pouch abandoned it about 1.5 years ago and joined the others in our group in using the "J" pouch. The "J" pouch, we believe, is more easily fashioned.

I would like to ask the Mayo people who I know have had experience with straight end-on anastomoses and with the "S" pouch, why they have chosen to use the "J" pouch? Has there been something they have learned that has put them into the "J" pouch field?

The results of our work have been very similar to the results reported today from Mayo. We have a 15% incidence of pouchitis. One incidentally was in a patient with familial polyposis whose ileostomy had not yet been closed. I certainly do not have an understanding as to why people get pouchitis.

Pelvic sepsis occurred in 4% of our patients, all of whom had inflammatory bowel disease. The other problems with the pouch, which include leak at the staple line, leak at the ileoanal anastomosis and anal stricturing, resulted in the occurrence of some type of pouch problem in nearly one quarter of our patients. Fortunately, most of these problems have been resolved.

As with the Mayo experience, our patients have been functionally satisfactory. They average five bowel movements in 24 hours and less than one of these movements occurs at night.

The sexual function of our patients has been somewhat better than that reported by Mayo, but on the other hand, we, the doctors, were doing the questioning, and patients go out of their way to try to please the doctor. Perhaps the impartial observer approach used by Mayo Clinic would be a better test of true function.

Twelve per cent of our patients, whether males or females, have ended up having a pregnancy after our operation.

The operation, we believe, is a great operation. It is now the operation of choice. In 1980 and 1981, we did three cases each of those years. This past year we did in excess of 70.

I would like to ask the authors some questions. Despite a large experience with inflammatory bowel disease, we frequently make the mistake of operating on a patient with ulcerative colitis only to find that clinically and histologically they have Crohn's disease. Did they have a problem with this in their patients reported today? And was there a relationship between complications and Crohn's disease?

Is there a difference in the results of your patients reported today with ulcerative colitis from those who you have treated for familial polyposis, especially in respect to complications?

I know that you have removed some pouches, and I wonder in your removal of these, what have you found histologically about regeneration of mucus membrane? Dr. Ravitch a few years ago reported that Dr. Snyder had noted a case of carcinoma in a person having this procedure done. In investigating this further, Dr. Ravitch, I have found that that patient had an anal canal cancer and not an adenocarcinoma. Nevertheless, the risk of regenerating mucosa and its neoplastic tendency is something that needs our constant concern.

DR. HEBER H. NEWSOME, JR. (Richmond, Virginia): Our series is smaller than that of the Mayo Clinic, as is every other series, but an important question has been addressed that I believe is the age factor.

You mentioned that the stool frequency was higher in the age over 50. We are surprised that the soilage rate is not higher because the sphincter, in our experience, tends to relax slightly as age progresses.

The direct question is have you measured sphincter function in older people? Could you give us a little more detailed breakdown of your data in the older population? Is there an age limit that you might use to exclude patients?

DR. KEITH A. KELLY (Closing discussion): First of all, I would like to thank the discussants for their thoughtful comments on our paper.

To start with Dr. Coran's questions, we obtained our follow-up data using an independent observer, a nurse practitioner. She contacted all the patients at periodic intervals and elicited, we believe, a more objective follow-up than we, the patients' physicians, could have done.

The endorectal dissections were all accomplished *via* the perineal approach. None were done *via* the abdominal approach. The anus was dilated slightly, and a small Gelpe retractor was used in the anal canal to provide access to the rectal lumen. We resected the mucosa from the dentate line to a point about 4 or 5 cm proximal to the line. The rectum was transected at that point, and more orad portions removed entirely.

Dr. Coran wonders whether there were times when the "J" pouch could not be used. In answer to that there were. In about 4% of patients, a "J" pouch would not have reached the dentate line. In these patients an "S" pouch was used. Another 2 or 3 cm in length is possible with the "S" pouch.

The disadvantage of the "S" pouch, is that its efferent limb may obstruct outflow from the pouch. Some of our "S" pouch patients have had to use a catheter to empty the pouch. In contrast, all of our patients with a "J" pouch can empty the pouch voluntarily and spontaneously.

Eric Fonkalsrud raises a number of good points. I certainly agree with him that this operation is not perfect as yet. We need to continue to explore methods of improving it. He wonders whether "pouchitis" might be due to a mechanical problem either at the ileal pouch–anal anastomosis or within the pouch itself. Our data suggest, however, that this may not be the case. We have seen terminal ileal inflammation in individuals with a straight ileoanal anastomosis (no pouch) and with no mechanical obstruction. Also, the incidence of pouchitis is much less in patients with familial polyposis, and yet such patients would be subject to the same mechanical problems as those with ulcerative colitis. Lastly, we have studied the emptying of the "J" pouch using scintigraphic techniques, and found that those patients with pouchitis emptied their pouches just as well as patients who had no pouchitis. Therefore, it seems unlikely that pouchitis is solely a mechanical problem. My own hunch is that pouchitis may arise in some way from an interaction between the luminal bacterial or their products and the intestinal wall.

Dr. Fonkalsrud wonders whether we are making our rectal mucosal cuff too short and, therefore, predisposing our patients to sexual problems. We stay close to the rectal wall during the pelvic dissection and away from the sympathetic and parasympathetic nerves innervating the bladder and genitalia. We make our cuff 4–5 cm in length. Perhaps by making it longer, we would preserve sexual function better.

We have not as yet tailored the operation to specific anatomic differences among the patients. Our goal was to create a pouch with a capacity similar to that of the normal rectum, which is around 350–400 mL. The "J" pouch does this quite well. Perhaps as we study our subjects further, we can identify patients in whom special tailoring should be done.

Dr. Veidenheimer asked why we make the "J" pouch rather than other types of pouch. We believe the "J" pouch is the easiest pouch to make. It can be constructed using sutures in about 15 minutes or using staples in about 10 minutes. The "J" pouch has an adequate size. It empties well without the need for a catheter.

He raises the difficult question about what do we do with patients who have Crohn's disease or in whom we cannot clearly rule it out. It is not always easy to separate Crohn's and ulcerative colitis, even when all the data are in. We discuss the possibility of "indeterminant colitis" with the patients before operation, and explore their opinion on what they want to do if their colitis cannot be clearly separated from Crohn's colitis. Nearly all patients want to proceed with the ileal pouch–anal operation and take their chances. That is usually what we end up doing.

We have observed patients with indeterminant colitis who have had the operation. They generally have done well. Thus, it is interesting to speculate as to whether or not we should explore the use of this operation in patients with Crohn's disease limited to the large intestine.

Are there differences between the responses of colitis patients to operation and the responses of patients with familial polyposis? Yes, there are. Fewer postoperative complications occur in familial polyposis patients. For example, no cases of pelvic sepsis occurred in our series of polyposis patients. Interestingly enough, the stool frequency is nearly identical as we observe both groups for several years after operation.

Have we left rectal mucosal behind, that could possibly predispose patients to long-term problems with carcinoma? We have removed the pouches of 24 patients who had a poor result from the operation. We looked at the specimens carefully for evidence of residual rectal mucosa. In about 15% we found small nests of residual rectal mucosa between the ileal pouch and the rectal tunica muscularis. Whether or not these nests would turn into cancer over the long term is unknown. The nests are not exposed to the luminal flora or to luminal carcinogens. Also, the amount of mucosa left is extremely small, making the chance of developing a cancer also small.

A question on age limit was asked. We started out saying nobody over 50 years, but then we had a healthy 55-year-old who asked, "What about me? I would like the operation." Therefore, we operated on this patient, and then we operated on a 60-year-old and then a 62-year-old. Our oldest patient is 64 years old. If older patients have a strong anal sphincter and healthy digestion and absorption, they should be considered. We have not operated on anyone over age 65 as yet.

I would like to close by thanking the members of the Association who have done so much to bring this operation forward; especially, Dr. M. Ravitch, Dr. D. Sabiston, Dr. L. Martin, and Dr. O. Beahrs, who did the first of these operations in adults at the Mayo Clinic.

Delayed Surgery and Bone Marrow Transplantation for Widespread Neuroblastoma

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From 1983 to 1986, 21 patients with poor prognosis neuroblastoma were treated with bone marrow transplantation. This regimen included induction chemotherapy, delayed surgical resection, local irradiation, and intensive chemoradiotherapy followed by infusion of allogeneic or autologous marrow. This therapeutic approach resulted in a 57% long-term survival rate (follow-up: 14–48 months), which appears to be approximately three times superior to conventional chemotherapy in a comparable group of children. In addition, complete resection was possible in 11 of 17 patients operated on after induction therapy. Recurrence in the primary site after bone marrow transplantation occurred in only one of 18 evaluable patients. Thus, this approach almost always eradicates primary tumor in patients with neuroblastoma with advanced disease.

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THE MAJORITY OF PATIENTS with neuroblastoma are found to have widespread disease at diagnosis. Their survival, if they are older than 1 year, is less than 10% with conventional therapy.[1] Surgery, which is important for the successful outcome of patients with localized disease, has not been shown to improve survival for children with widespread involvement.[2–4] Two factors most likely responsible for these poor results are the inability to perform complete surgical resection because of widespread disease and the inability of chemotherapy to control metastatic disease.

Recent advances in multimodal therapeutic approaches for Stage III and IV neuroblastoma have resulted in some improvement in the survival rate. Complete surgical resection of the primary tumor has been facilitated by delaying the definitive operation until after initial chemotherapy. This approach has been useful in the treatment of other tumors and has been shown to affect survival for patients with neuroblastoma who have a large primary tumor with minimal or no metastases.[5–8] Bone marrow transplantation (BMT) has also been reported to improve clinical outcome of patients with widespread neuroblastoma.[9–11] This regimen includes induction chemotherapy, delayed surgery, interim chemotherapy, and autologous or allogeneic bone marrow transplant.

The purpose of this study was to determine (1) resectability of primary neuroblastoma after induction chemotherapy; (2) sites and frequency of tumor recurrence after multimodal therapy and BMT; and (3) the toxicity and efficacy of BMT.

Materials and Methods

Patients

Neuroblastoma was diagnosed according to standard clinical and pathologic criteria. Stage III disease was defined as primary tumor extending in continuity beyond the midline with or without bilateral regional node disease. Stage IV disease included all patients with remote tumor involving multiple sites such as bone, bone marrow, organs, soft tissues, or lymph nodes. Patients were eligible for study if they were over 1 year old but less than 19 years old at the time of diagnosis and if they had Stage IV or poor prognosis Stage III disease. Patients

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with poor prognosis Stage III disease included those with elevated serum ferritin (greater than 142 ng/mL),[12] increased N-*myc* oncogene copy number (more than 10 as determined by Southern analysis of DNA from primary tumor),[13] or unfavorable tumor histopathology (Schimada classification).[14]

The transplanted patients were divided into two groups, both of whom initially received conventional chemotherapy. Group 1, which included two patients with Stage III disease and 12 patients with Stage IV disease, received intensive chemotherapy and were transplanted before progressive disease developed. Group 2, which comprised seven patients with Stage IV disease, had already developed progressive disease when they received intensive chemoradiotherapy and transplant. Progressive disease was defined as either regrowth of primary tumor, new bone metastases, or one log increase in bone marrow metastases before pretransplant chemoradiotherapy.

Induction Chemotherapy

All 21 patients who had transplantation received conventional chemotherapy initially. Although induction therapy consisted of many regimens, most patients received combinations of the following drugs: cyclophosphamide, vincristine, dacarbazine, doxorubicin, teniposide, and cisplatin.

Surgery and Local Irradiation

Operation was performed to aid in the initial diagnosis and/or before bone marrow transplantation. If definitive surgery was performed at the time of diagnosis, debulking was attempted. Otherwise the operation was deferred until after induction chemotherapy. Delayed operation was not performed if patients were considered unresectable or if computed tomography and/or magnetic resonance imaging demonstrated complete response of the primary tumor to chemotherapy. After recovery from operation, another course of chemotherapy was administered to prevent tumor recurrence immediately before transplant.

Local irradiation was given to all patients with residual primary or metastatic tumor. For residual primary tumor, radiation was delivered to the tumor bed as outlined by surgical clips. If the tumor was deemed inoperable than total abdominal or thoracic radiation (with shielding of uninvolved lung fields) was administered. For metastatic disease, radiation was delivered to bone lesions that were positive by both technetium scan and skeletal survey. A total dose of 10 Gy was given to abdominal sites and 20 Gy to nonabdominal sites (2 Gy/day on consecutive days).

TABLE 1. *Pretransplant Intensive Chemoradiotherapy Regimen (VAMP-TBI)**

Days Before Transplant	Therapeutic Agent
−9	Cisplatin, 90 mg/m^2 IV
−8	No therapy
−7	Teniposide, 150 mg/m^2 IV, doxorubicin, 45 mg/m^2 IV
−6	L-phenylalanine mustard, 140 mg/m^2 IV
−5	L-phenylalanine mustard, 70 mg/m^2 IV
−4	Teniposide, 150 mg/m^2 IV
−3	TBI, 333 rad, 8–10 rad/min
−2	TBI, 333 rad, 8–10 rad/min
−1	TBI, 333 rad, 8–10 rad/min

* For patients less than 2 years old or weighing less than 12 kg, the doses of agents was changed to cisplatin, 3.5 mg/kg; doxorubicin 1.7 mg/kg; L-phenylalanine mustard, 5.4 and 2.7 mg/kg; teniposide, 5.8 mg/kg.

Pretransplant Intensive Chemoradiotherapy

This consisted of teniposide, doxorubicin, L-phenylalanine mustard, and cisplatin from days −9 to −3 and fractionated total body irradiation (10 Gy total dose, 3.33 Gy/day at a rate of 5–10 cGy/min on days −3, −2, and −1 (day 0 equals day of marrow infusion) (Table 1).

Bone Marrow Harvest

Marrow harvesting was performed on the anterior and posterior iliac crests bilaterally under general anesthesia in the operating room (average time 60 minutes). A cell count of the removed marrow was performed during the procedure to ascertain the volume of marrow to be extracted. Allogeneic recipients received the marrow transplant on the day of harvest. Autologous recipients had their marrow harvest usually at the time of delayed operation for tumor resection (under the same anesthesia), which was 4–8 weeks before transplant. Storage of the marrow was achieved using standard cryopreservation techniques (liquid nitrogen).[15]

Bone Marrow Transplantation

Nine patients received bone marrow from HLA-MLC matched, nonidentical siblings. The average number of nucleated marrow cells infused was 3×10^8/kg. Infusion of marrow was *via* a central venous catheter over 60–90 minutes. These patients were given methotrexate after BMT for prophylaxis of graft *versus* host disease (10 mg/m^2 on days 1, 3, 6, 11, and then weekly to 100 days).

Twelve patients had no histocompatible donor and therefore received autologous marrow. No tumor cells were detectable by immunoperoxidase staining with antineuron-specific enolase serum and antineuroblastoma cell surface monoclonal antibodies (antibodies 390,

TABLE 2. *Sites of Primary Tumor*

Site	No. of Patients
Abdominal	
Adrenal	12
Extra-adrenal	3
Thoracic	3
Pelvic	2
No primary found	1

TABLE 3. *Resection of Primary Tumor for Neuroblastoma*

	At Diagnosis	Delayed
Complete	2	3*
Partial (>50%)	3	2
Partial (<50%)	0	2
Biopsy only	3	0
Not done	13	4

* No tumor present at operation for two patients.

HSAN 1.2, 459, and 126-4). The limit of sensitivity of this test is one neuroblastoma cell per 10^5 normal cells when 3×10^5 bone marrow mononuclear cells are evaluated.[16] Preparation of autologous marrow included: equilibrium density centrifugation over Ficoll-Hypaque (seven patients); sedimentation with Hetastarch and filtration through nylon wool (one patient); and sedimentation, filtration, and incubation with monoclonal antibodies (antibodies 390, 459, HSAN 1.2, BA-1, and RB 21-7 or 459, BA-1, and 126-4) and goat antimouse immunoglobulin coated with magnetic beads (four patients, two of whom had marrow involvement at harvest). Autologous recipients were given 1×10^8 nucleated marrow cells per kilogram. The exact methodology for harvesting, cryopreservation, and infusion of bone marrow has been previously reported.[17] No further therapy was given after transplantation.

Recovery phase

Patients were placed in strict isolation once the absolute neutrophil count was below 500/mm^3. All patients received broad-spectrum antibiotics once they had a fever greater than 38 C during strict isolation. Patients were removed from isolation once their absolute neutrophil count reached 500/mm^3 for 3 consecutive days (approximately 4–5 weeks after marrow infusion). Platelet and hemoglobin levels were maintained at 30,000/mm^3 and 12 g/dL, respectively. Platelet transfusions were administered every 2–4 days, and packed red cell transfusions were given every 3–5 days for approximately 6 weeks in accordance with our protocol developed for bone marrow transplantation in leukemic children.

Results

Disease Status at Diagnosis

There were 19 patients with Stage IV disease, 18 of whom had marrow disease. All of these children had involvement of distant bones. There were two patients with Stage III disease, one of whom had occult marrow involvement at the time of bone marrow harvest. The age at diagnosis ranged from 14 months to 13 years with a mean of 4.9 years. The primary tumor sites are listed in Table 2.

Surgery

A summary of operative results is shown in Table 3. For primary tumor at diagnosis, resection was attempted for eight patients: complete resection was achieved for two patients, partial resection with gross tumor remaining was performed for three patients, and biopsy only was done for three patients. Delayed resection of the primary tumor was performed on 17 patients: complete resection was possible for 11 patients, partial resection with less than 50% of gross tumor remaining was performed for two patients, partial resection with greater than 50% gross residual tumor was performed for two patients, and no tumor was found for two patients, both of whom had complete resection of primary tumor at the first operation. Delayed operation was performed within 3 months before BMT for 13 patients. Four patients had surgery at an earlier time (9, 12, 18, and 26 months before BMT), none of whom displayed evidence of primary tumor recurrence at the time of transplant.

Toxicity and Fatal Complications during the First Month after BMT

Toxicity included severe oral mucositis, enteritis, and skin desquamation and was worse among patients receiving allogeneic marrow. Death occurred in five patients during the first month after transplantation. The causes of these early deaths were renal failure (2 patients), hepatic veno-occlusive disease (1 patient), disseminated candidiasis (1 patient), and bacterial sepsis (1 patient). All of these deaths occurred before documented engraftment. Autopsy performed on four patients did not demonstrate residual primary or metastatic tumor.

Late Complications

One patient receiving autologous marrow failed to successfully engraft with platelets and died of cerebral hemorrhage 3 months after BMT. One patient died of bacterial infection 3 months after transplantation. Both patients did not have residual primary or metastatic tumor at autopsy.

Survival/Relapse

Fourteen transplant recipients survived more than 3 months after transplant and were considered to be at risk for relapse. Twelve of these patients had delayed operations, nine of whom had complete resection. Relapse and subsequent death occurred in six patients (between 4 and 10 months after transplant), and only one patient, who had less than 50% resection, had viable primary tumor at autopsy. The remaining eight patients, two of whom did not have delayed surgery, are surviving 14–48 months (median: 32 months) after transplant. Two relapses occurred in these patients (12 and 18 months after transplant) and subsequent remission was achieved in one patient with further chemotherapy, whereas the other patient is alive with stable disease. Summary of the sites of tumor relapse are shown in Table 4.

Transplant before Progressive Disease Versus *after Progressive Disease*

We analyzed disease-free survival for two groups of patients: those transplanted before their disease had progressed and those transplanted afterwards. All disease-free survivors are in the group transplanted before development of progressive disease (Table 5). Overall survival is 57% for patients transplanted before progressive disease *versus* 0% for patients treated after progressive disease ($p < 0.001$). Patients with progressive disease before transplantation were generally older and further from diagnosis. At this time there does not appear to be an advantage of either autologous or allogeneic transplant with respect to disease-free survival (Table 5).

TABLE 4. *Tumor Recurrence Sites after BMT*

	N
Primary	1
Bone	8
Bone marrow	8
Number of patients	8

TABLE 5. *Outcome of Patients Undergoing BMT*

Therapy Group	No. of Patients	No. Surviving	No. Surviving Disease-free
BMT before PD			
Autologous	10	6	5
Allogeneic	4	2	2
BMT after PD			
Autologous	2	0	0
Allogeneic	5	0	0

Discussion

Complete resection of the advanced primary neuroblastoma is facilitated by induction chemotherapy. These findings confirm previous reports that surgery performed after initial chemotherapy is more effective for removal of primary tumor.[3,5–8] Combining delayed surgery with local irradiation and intensive chemoradiotherapy is effective for eradicating primary tumor, and appears to result in improved survival.

The overall survival of our patients compares favorably with previous reports of bone marrow transplantation for poor prognosis neuroblastoma. Pritchard et al.[9] reported three long-term disease-free survivors of 12 children who received autologous transplants after high-dose melphalan. August et al.[10] reported four long-term survivors of 10 patients transplanted after multiagent conditioning. Our findings combined with these published results suggest increased efficacy of bone marrow transplantation compared with conventional chemotherapy for widespread neuroblastoma.

The most important factor for determining outcome was the timing of the transplant. All patients transplanted after progression of disease died of toxic complications or tumor relapse. These children had in general received more therapy before transplantation and this may have contributed to poorer tolerance to the intensive chemoradiotherapy conditioning regimen. Also, neoplastic cells resistant to conventional chemotherapy may be less responsive to intensive therapy.

Toxic mortality associated with the intensive chemoradiotherapy (VAMP-TBI) was acceptable for autologous but not for allogeneic marrow transplantation. The increased toxicity after allogeneic transplantation is probably due to methotrexate and graft *versus* host disease. Because of the excessive toxicity in this and a larger series,[11] we do not recommend VAMP-TBI for allogeneic BMT. Less toxic regimens currently are being tested.

Our data indicate that the combination of delayed operation, local irradiation to residual tumor, intensive chemoradiotherapy, and bone marrow transplantation is an effective means of eradicating primary tumor in widespread neuroblastoma. Overall survival appears to be improved compared with conventional chemotherapy.[11] Current studies include the use of aggressive induction chemotherapy, surgical removal of the primary tumor at 16 weeks, intensive chemoradiotherapy and transplantation at 20 weeks, and removal of residual neuroblastoma cells from autologous marrow. These new approaches will hopefully improve the long-term outcome for children with neuroblastoma.

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DISCUSSION

DR. JAY L. GROSFELD (Indianapolis, Indiana): We have been interested in this tumor for many years and reviewed our own cases of neuroblastoma at the James Whitcomb Riley Hospital for Children at Indiana University. We have treated 248 patients and, unfortunately, over 70% of the children have extensive disease at diagnosis.

Unlike Wilm's tumor where chemotherapy can actually achieve a cure, there has been no clear objective evidence to suggest that chemotherapy cures patients with neuroblastoma. Cellular kinetic studies indicate that the vast majority of the neuroblastoma cells are in a resting phase and, therefore, are not amenable to tumor kill with convention chemotherapy and irradiation. Therefore, the authors have taken a more intensive chemoradiation approach in attempts to cure metastatic disease.

Resection of a primary cancer in patients with metastases has always been somewhat controversial. In support of the author's observations, however, we have noted that none of our Stage IV (metastatic) patients have ever survived if the primary tumor was not resected. Residual disease is usually found at delayed primary or second-look laparotomy despite chemotherapy.

We have had a number of Stage IV patients who responded to chemotherapy, had extended survival (5–6 years), and then late recurrence with subsequent death. The relatively small number of patients in this study leads us to question the authors' conclusions that 50% of these high-risk patients with metastases will survive.

The data presented document an increase in the length of survival, but is the actual cure rate being changed?

Unfortunately, our experience with bone marrow transplantation for neuroblastoma has not been as encouraging as the authors'. On the other hand, most of our patients have been transplanted because of relapse or progressive disease. The important point that our colleagues have told us is that you cannot wait for progression of disease to occur if you expect to attempt to cure the patient with a bone marrow transplant.

In reviewing their data, an unfortunate fact is that seven of the 21 patients (33% mortality rate) died as a result of treatment.

Of the remaining 14 patients, six relapsed soon after intense therapy, and of the eight late survivors, there were another two cases of relapse. Invariably, patients who relapse usually die. One might anticipate more relapses with time.

The validity of the statistical data is questionable because of the small number of patients and the relatively short length of follow-up.

I have some questions for the authors. Did relapse occur in the two patients with tumor demonstrated in the autologous bone marrow? Was the technique of using monoclonal antibodies successful in purging the marrow? In your selection of Stage III patients, is site an important factor? For instance, should Stage III patients with primary tumors in the neck or pelvis be grouped in the same fashion as patients with primary tumors at the celiac axis? At our institution, all Stage III neck and pelvic patients have survived with conventional therapy. I would hesitate to subject those patients to potentially lethal chemoradiation and bone marrow transplantation. Has DNA aneuploidy or diploidy been an important flow cytometry observation in your patients? Is this used in the selection process?

Only time will tell if this new intense treatment is just another frustrating attempt to chase metastatic cancer or whether this will improve the cure rate of this troublesome, pediatric tumor. Cure for metastatic neuroblastoma is a goal that thus far has been most elusive.

DR. JAMES A. O'NEILL, JR. (Philadelphia, Pennsylvania): I congratulate Drs. Moss, Fonkalsrud, and their coauthors for bringing this to the attention of a surgical audience as well as for their results. Dr. Moss is a pediatric oncologist, and this sort of paper is not frequently presented at surgical meetings; yet, it is extremely valuable that we hear about it.

This study addresses a significant problem in neuroblastoma patients since most have Stage IV or what we would call metastatic disease. You should know that their study was one of the first, if not the first, to use this particular regimen described.

My own comments are based on 38 patients with neuroblastoma treated at the Children's Hospital of Philadelphia in virtually the same fashion except for minor variations in chemotherapy approach. The results have been tabulated as of November 1986.

Our results would generally support your conclusion as you looked at your primary goals, that resectability of primary disease can be enhanced with this regimen, and that when relapse occurs, it is usually elsewhere other than the primary site.

You also have shown the effects of toxicity of this intensive regimen in patients who have bone marrow transplantation. However, I am not sure that either you or we have proven the efficacy of bone marrow transplantation. If we take your figures, your overall survival at 3 years is 8 of 21 patients or 38%. If we take our figures at 3 years, it is 15 of 38 patients, or 39%, which is almost identical. However, if one considers our patients who are alive with disease and consider them nonsurvivors, our estimation is that our long-term survival rate is going to be in the range of 25%. Would you comment on that particular point?

Second, as you did, we had a number of early deaths due to toxicity, and many of these were infectious in nature. It is here that we must improve our results, and perhaps this is where we have some hope.

In this respect our results have been so poor with allografts because of graft-versus-host disease and the methotrexate necessary to accomplish allografting in these patients, we have virtually abandoned this approach in favor of autogenous grafting and purging harvested marrow of tumor cells with monoclonal antibodies and then magnetic immunobeads that you have heard about. I might add parenthetically we have one well-functioning syngeneic graft.

Regarding the matter of these allograft problems, although I believe that you have pointed out something very valuable regarding the futility of bone marrow transplantation in patients with neuroblastoma and progressive disease, I have some concern about the figures, in that as one looks at the allograft–autograft component of each group, you have 4 of 14 patients who were transplanted before progressive disease with allografts and 5 of 7 in the group that were transplanted with progressive disease. Obviously, I am concerned that this factor of a greater number of allografts in the progressive disease group could well have biased your conclusion about the futility of transplanting patients with progressive disease.

Did you find a difference in results in patients with favorable *versus* unfavorable Shimada histology? Our own results would tell us that histology is the most important determinant of survival in patients with localized disease, that is, Stages I through III.

Finally, did patients who had complete resection of the primary tumor fare better than those who did not? In other words, did surgery make a difference? It seems to in localized neuroblastoma patients.

I believe this is an extremely important paper of a pioneering nature, and particularly for surgeons, with excellent data and results.

Dr. Paul S. Russell (Boston, Massachusetts): My experience with this is rather antiquated because back in the late 1950s we became interested in autologous bone marrow transplantation for acute lymphatic leukemia in children. Since that time, the chemotherapeutic regimens have improved greatly.

We wrote a paper about our approach in the *New England Journal of Medicine*, in 1959.[1] What we did was to harvest the marrow from patients who had drug-induced remission at a time when this marrow and peripheral blood was in a remarkable state of morphological normality. The bone marrow was then frozen and kept until later relapse of the disease. Patients were then given whole body irradiation in the lethal range and the bone marrow was reinfused. We had some nice remissions. We had a short series of patients with leukemia, I believe about half a dozen, but we also had one additional patient who had a neuroblastoma with dissemination.

My questions relate to the source of the marrow. If one uses autologous marrow it must be purged of the malignant cells. If the marrow comes from an allogeneic source, unless you are fortunate enough to have an HLA identical donor, it must be purged of potential graft-versus-host producing "T" lymphocytes by another form of purging. How good are you at purging the marrow of malignant cells from autologous donors? If this can be done reliably it would provide a treatment that could be used for a large number of patients, whereas with allogeneic marrow, you will encounter the dangers of immunosuppression and graft-versus-host disease.

It looks to me as if the way to go is to focus on trying to get rid of any malignant cells that are in the autologous marrow, perhaps saving it in the frozen state.

Reference

1. McGovern JJ, Russell PS, Atkins L, Webster EW. Treatment of terminal leukemic relapse by total-body irradiation and intravenous infusion of stored autologous bone marrow obtained during remission. N Engl J Med 1959; 260:675–683.

Dr. Stanley R. Friesen (Kansas City, Kansas): I noticed on your slide regarding prognosis that you had neurone-specific-enolase as a prognostic factor. I have considered that enzyme as a characteristic diagnostic feature of these kinds of tumors. I did not realize that it had a prognostic influence. Is the neurone-specific-enolase that you describe that which is present in the tumor or that which is circulating in the plasma?

Dr. Thomas J. Moss (Closing discussion): I would like to thank Drs. Grosfeld, O'Neill, Russell, and Friesen for their enlightening comments and questions.

Dr. Grosfeld, in terms of the late relapses, we share your concern since this may occur with neuroblastoma. As you indicate, our longest survival is 4 years, the longest survival reported thus far is 5 years. The international experience with bone marrow transplant and relapse is that the latest relapse thus far reported is 22 months after transplant. This does not mean that relapse will not occur within 3 or 4 years after transplant. We have to be guarded in our conclusions because of this, and we are evaluating this issue closely.

In terms of relapse in the autologous marrow, there was one relapse in a patient who had tumor cells removed at harvest. That patient relapsed first in bone, and then in bone marrow.

In the autologous marrows that were separated with Ficol Hypaque alone in which we did not remove tumor cells, there was relapse in approximately two thirds of those patients; across the country, it appears that two thirds of those patients had relapse in bone marrow first. From this experience, our concern was that we may be reinfusing tumor cells into the patient at transplant, and we therefore started our purging technique.

In terms of Stage III patients, we only selected two patients thus far. They were not selected by primary tumor site but by prognostic factors. These factors included increased serum ferritin, increased N-*myc* oncogene copy number and poor prognosis histology (Shimada classification). These patients have a survival rate of less than 20% with conventional therapy.

One of our stage III patients did have amplification of the N-*myc* oncogene; he was recently transplanted and is now alive at 14 months.

When the study was first started, the determination of N-*myc* oncogene was not performed. We are currently doing it in all patients. About one third of our patients have amplification of the N-*myc* oncogene, and we hope not to select out for that group because we want to see if our therapy can make a difference. It is too early to tell at this time.

Dr. O'Neill, you raise an important point about overall survival. Progressive disease is an important variable. The chemotherapy group was a nonrandomized but concurrent control group; we tried to make the control group as comparable as possible with the transplant group. The chemotherapy group chosen were those patients who had not developed progressive disease at 7 months after diagnosis. We picked that point because our transplant patients, who were transplanted before progressive disease, were on the average transplanted 7 months after diagnosis, therefore we hoped to remove that one variable. Unfortunately, with retrospective analysis one also has to be cautious in the judgments that one makes. It does seem that we can eradicate primary tumor with this regimen. I view this as a consolidation therapy.

The next step is defining the maintenance therapy after bone marrow transplant. We are exploring the use of retinoic acid, which is a differentiating agent. It has minimal toxicity and may differentiate those last few neuroblastoma cells that are present after transplant. This is a strange tumor that regresses sometimes without any reason; can retinoic acid be one way to induce a lasting remission? Retinoic acid does cause decreased expression of the N-*myc* oncogene, and we have studies to prove this. We are hopeful that this type of maintenance therapy, which has little toxicity, will prove useful.

Another possibility is treatment with monoclonal antibodies. There is an antibody to the GD_2 ganglioside that is relatively specific for neuroblastoma. It is currently being evaluated for therapy of patients who have developed progressive disease. It does have some efficacy, but, will this play a part in the maintenance therapy after bone marrow transplant? We are currently initiating studies to look at this particular treatment.

In terms of allogeneic toxicity, this is a valid and important point. We have recently become aware of this problem; approximately 50% of allogeneic transplants have a toxic death. Consequently, the Children's Cancer Study Group has decreased the methotrexate dose given to prevent graft-versus-host disease, and we also are altering the chemoradiotherapy regimen to make it less intense to see if this will reduce toxicity. We hope these changes will not alter tumor relapse, therefore we are wary of doing allogeneic transplants at this time.

In terms of autologous transplants, our toxicity is running about 10%, and we hope that if we can reduce relapse, autologous transplant may be the therapy of choice in the future. Conversely, allogeneic transplants do seem to have less relapse, but there are too few patients to even make a meaningful comment. In terms of overall survival, including those from other institutions in the country, this does seem to be holding as a general trend, but we will be cautious in our determination of what the ultimate outcome is.

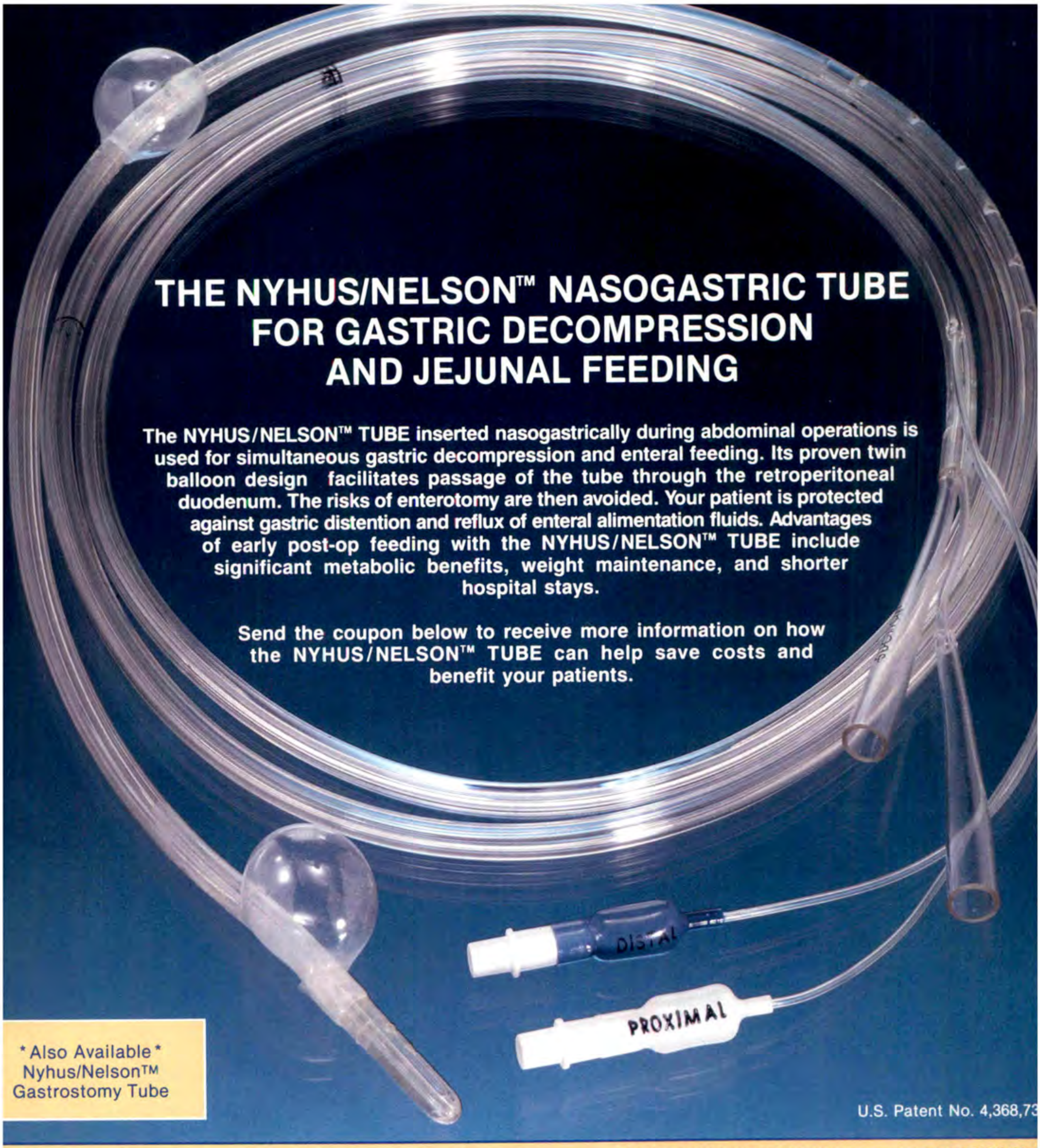
The vast majority of our patients had unfavorable histology, and we were unable to evaluate this factor compared with favorable.

Does surgery make a difference? There are too few patients to tell. Of the survivors, two had partial resection; the rest had complete resection. I believe surgery plays an important role for Stage III disease. This is one important point of the study, that delayed surgery does facilitate complete resection. It does point out that we are having problems in controlling bone and bone marrow metastases.

Dr. Russell, in terms of autologous bone marrow transplant and removal of the tumor cells we have developed an immunohistologic method to detect neuroblastoma cells in bone marrow. Of the five patients who we treated, two had demonstrable tumor in the harvested bone marrow. We can detect one tumor cell among 100,000 normal marrow cells. Since we infuse 10^9 cells per patient at transplant, we could infuse 10,000 tumor cells and not even know the difference. That is why we instituted the tumor purging. We can remove four logs of tumor cells experimentally with purging. We have done approximately 22 autologous purged marrows at this point, and we are able to clean out bone marrow consistently that has under 1% of tumor cells, although that may be a little optimistic in the sense that we have probably gone below the sensitivity of our testing. Significantly, of the 22 harvests, approximately 17 had tumor cells detected, which would have been ineligible for our previous study. We can now purge and remove these cells to allow these patients to be transplanted.

How many tumor cells will cause recurrence of tumor if infused? No one knows the answer. That is why maintenance therapy will be so important.

Finally, Dr. Friesen, neuron-specific-enolase (NSE) is of prognostic value for patients with Stage IV disease under one year of age, and it is an independent variable.



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Causal Relationship Unknown: The following other adverse reactions have been reported in clinical trials. While a causal relationship could not be established for these infrequently reported events, causality cannot be excluded. *Body as a Whole*—Fever, asthenia, fatigue. *Cardiovascular*—Palpitations. *Gastrointestinal*—Nausea, vomiting, abdominal discomfort, anorexia, dry mouth, liver enzyme abnormalities. *Hematologic*—Thrombocytopenia. *Hypersensitivity*—Orbital edema, conjunctival injection. *Musculoskeletal*—Musculoskeletal pain, arthralgia. *Nervous System/Psychiatric*—Paresthesias; grand mal seizures (single report); psychic disturbances including depression, anxiety, decreased libido, hallucinations (single report); insomnia; somnolence. *Respiratory*—Bronchospasm. *Skin*—Alopecia, acne, pruritus, rash, dry skin, flushing. *Special Senses*—Tinnitus, taste disorder.

The adverse reactions reported for PEPCID Tablets may also occur with PEPCID Oral Suspension or PEPCID I.V.; in addition, transient irritation at the injection site has been observed with PEPCID I.V.

Management of Overdosage: There is no experience to date with deliberate overdosage. Up to 640 mg/day have been given to patients with pathological hypersecretory conditions with no serious adverse effects. In the event of overdosage, treatment should be symptomatic and supportive. Unabsorbed material should be removed from the gastrointestinal tract, the patient should be monitored, and supportive therapy should be employed.

Dosage and Administration: ***Duodenal Ulcer:*** The recommended adult oral dosage for active duodenal ulcer is 40 mg h.s.; most patients heal within 4 weeks, and it is rarely necessary to use the full dosage for longer than 6 to 8 weeks. A regimen of 20 mg b.i.d. is also effective. For maintenance therapy, the recommended oral dosage is 20 mg h.s.

Pathological Hypersecretory Conditions (e.g., Zollinger-Ellison Syndrome, Multiple Endocrine Adenomas): The dosage varies with the individual patient; the recommended adult oral starting dosage is 20 mg q6h, but some patients may require a higher starting dosage. Dosages should be adjusted to individual patient needs and continued as long as clinically indicated; up to 160 mg q6h have been administered to some patients with severe Zollinger-Ellison syndrome.

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Stability of PEPCID Oral Suspension: Unused constituted oral suspension should be discarded after 30 days.

Intravenous Administration: In some hospitalized patients with pathological hypersecretory conditions or intractable ulcers, or in patients who are unable to take oral medication, the recommended intravenous dosage is 20 mg q12h. For preparation of solutions for injection or infusion and for compatible diluents, please see Prescribing Information. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

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Upper Extremity Ischemia Caused by Small Artery Disease

JOSEPH L. MILLS, M.D.,* ERIC I. FRIEDMAN, M.D.,† LLOYD M. TAYLOR, JR., M.D.,‡ and JOHN M. PORTER, M.D.§

From the Division of Vascular Surgery, Oregon Health Sciences University, Portland, Oregon

One hundred patients with ischemic finger ulceration had detailed prospective evaluation to determine the incidence of associated diseases, response to treatment, and natural history of the condition. A potentially serious associated disease was detected in each patient including autoimmune disease in 54%, Buerger's disease in 9%, arteriosclerosis obliterans in 9%, hypersensitivity angiitis in 22%, and miscellaneous diseases in 6%. Conservative treatment with soap and water scrubs, antibiotics, and local resection/debridement resulted in long-term healing without recurrence in 88% of patients. Most recurrences occurred in patients with autoimmune disease, usually scleroderma or CRST.

A MAJORITY OF PATIENTS with peripheral ischemia suffer from atherosclerotic occlusive disease of the large arteries supplying the lower extremity. It has been estimated that only 5% of patients with limb ischemia have symptomatic involvement of the upper extremity.[1] Ischemic digital ulceration or gangrene may develop in patients with severe upper extremity ischemia. Although large artery atherosclerosis is the most common cause of lower extremity ischemia, small artery occlusive disease of the palmar and digital arteries of diverse causes is a frequent cause of upper extremity ischemia.[2]

Upper extremity ischemia caused by small artery occlusive disease occurs with sufficient infrequency that little has been published describing its evaluation and treatment. The underlying small artery etiology in a patient with ischemic digital ulceration is often considered only after extensive evaluation fails to reveal proximal arterial obstruction or a cardiac or proximal arterial embolic source. Similarly, optimal treatment of upper extremity ischemia resulting from small artery disease has not been defined. Multiple investigators, usually citing anecdotal information derived from personal treatment of a small group of patients, have reported benefit from various forms of treatment, including vasodilators,[3,4] prostaglandins,[5] antiplatelet therapy,[6] and thoracic sympathectomy.[7] None of these is of proven benefit.

In the past 15 years, over 900 patients with vasospastic or occlusive small artery disease of the upper extremity have been prospectively evaluated and treated in the Clinical Research Center at The Oregon Health Sciences University as part of an ongoing research protocol conducted by the Division of Vascular Surgery. One hundred of these patients had upper extremity ischemia of sufficient severity that they presented with ischemic digital ulceration or gangrene. The prospectively accumulated data pertaining to this subgroup of patients have been reviewed to determine the incidence and distribution of underlying associated diseases, the tests that reliably diagnose associated diseases, the forms of treatment most likely to result in a favorable clinical response, and the natural history of the condition. The results of the review form the basis for this report.

Methods

The records of over 900 patients with small artery disease who have been prospectively evaluated, treated,

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TABLE 1. *Diagnostic Evaluation of Upper Extremity Ischemia*

	Routine	In Selected Patients
Laboratory	Complete blood count Urinalysis Sedimentation rate Automated chemistry (SMAC) Immunologic screen (Table 2)	
Radiographic	Chest film Hand films Magnification hand arteriography	Barium swallow Barium enema Intravenous pyelogram
Vascular laboratory	Finger and toe digital photoplethysmography Segmental upper and lower limb arterial pressures Nielsen test	Treadmill walking test Digital plethysmography after warming and cooling
Other		Skin biopsy Muscle biopsy Arterial biopsy Electromyogram Electrocardiogram

and enrolled in an ongoing investigational protocol in the Clinical Research Center (CRC) over the past 15 years were reviewed. A subset of 100 patients was identified who had at least one episode characterized by the occurrence of ischemic digital ulceration with full thickness skin loss or frank gangrene with extensive tissue necrosis. All patients had small artery obstruction documented objectively by digital plethysmography (obtained in 100% of patients) and magnification hand arteriography (performed in 75%).

Each patient was admitted to the CRC and had a detailed evaluation, which is outlined in Table 1. Each patient was carefully questioned in an effort to exclude known causes of digital artery occlusion such as frostbite,[8] repetitive trauma ("hypothenar hammer syndrome"),[9] accidental intra-arterial drug injection,[10] proximal embolic source,[11] drug ingestion (ergot intoxication),[12] and environmental toxin exposure, including heavy metals and vinyl chloride.[13] Signs and symptoms of connective tissue disease were specifically sought in the history and physical examination, including alopecia, xerostomia, xerophthalmia, aphthous lesions, dysphagia, arthralgias, arthritis, rash, myalgias, myopathy, and sclerodactyly. Palpation of peripheral pulses, palpation for cervical ribs and clavicular abnormalities, and auscultation of the supraclavicular fossa for bruits were routinely performed to identify potential embolic sources such as subclavian artery aneurysm or proximal atherosclerosis.

TABLE 2. *Immunologic Tests*

	Test
Essential	Rheumatoid factor (latex particle) Antinuclear antibody
Complete	Serum protein electrophoresis Cold agglutinins VDRL Hep-2 ANA Antinative DNA antibody Extractable nuclear antigen Total hemolytic complement Complement (C3, C4) Immunoglobulin electrophoresis Cryoglobulins (Cryocrit) Cryofibrinogen Direct Coomb's test HbS Ab: hepatitis B antibody HbS Ag: hepatitis B antigen

Upper extremity digital photoplethysmography and segmental arterial pressures and waveform recordings were obtained in all patients, as previously described.[14] Segmental leg arterial pressures and treadmill walking were performed if indicated by clinical history or abnormalities detected on physical examination. A digital hypothermic challenge test (Nielsen test)[15] was obtained in patients with a history of digital cold sensitivity. Arteriography using a transfemoral approach and selective catheter techniques, with views from the aortic arch to the fingertips, was performed in 75% of patients. Magnification hand arteriography as described by Rosch from our institution was routinely included.[16]

The laboratory evaluation of patients with small artery disease is outlined in Tables 1 and 2, and was directed toward the detection of serologic abnormalities associated with autoimmune diseases. The details and methodologies of these tests have been described.[17-19] Radiographic evaluation consisted of chest and hand roentgenograms in all patients. Barium swallow, barium enema, and intravenous urography were performed selectively based on the results of the history, physical, and laboratory evaluations. Patients with acute finger ulceration or gangrene were examined weekly in the CRC. Ischemic lesions were photographed on each visit. All patients were treated conservatively with soap and water cleansing, debridement of necrotic tissue, fingernail removal if required to facilitate drainage of infection, and culture-specific antibiotics. Delayed phalangeal amputation, when necessary, was performed to conserve maximal digital length. Numerous vasodilator medications were used to treat painful acute ischemia as well as chronic obstructive Raynaud's symptoms. No thoracic sympathectomies were performed. After initial healing, all patients were followed up permanently at 6–12-month intervals. Serial noninvasive vascular laboratory and serologic tests were obtained at each visit.

Results

Demographics

The study population of 100 patients consisted of 64 women and 36 men with a mean age of 46 years. Associated conditions and risk factors were frequent; 68% were cigarette smokers, 7% had hypertension, 9% were hyperlipidemic, and 5% had diabetes mellitus. Forty-one patients (41%) had acute onset of finger ischemia, whereas 59% had chronic upper extremity digital ischemia.

Plethysmographic and Angiographic Results

All patients had profound obstruction of the palmar and digital arteries documented objectively by photoplethysmography and arteriography. The diagnosis of small artery obstructive disease was made in each patient by the combination of normal arterial pressures and waveforms in all arteries proximal to the wrist, and obstructive digital photoplethysmographic waveforms in multiple fingers associated with multiple finger blood pressures at least 30 mmHg below brachial artery pressure.[20] No patient with finger ulceration had digital artery vasospasm alone. A representative tracing of a 24-year-old man with sudden onset finger ischemia and resultant ulceration secondary to hypersensitivity angiitis showed the typical flattened obstructive waveform characteristic of digital artery occlusion (Fig. 1). Magnification hand arteriography (Fig. 2) confirmed the presence of massive digital artery occlusions, with normal proximal arteries. In 25 patients, arteriography was deferred because plethysmography documented bilateral diffuse digital artery obstruction and an underlying connective tissue disease had been diagnosed according to the criteria stated.

Associated Diseases

Using the methodical evaluation outlined above, an underlying disease responsible for palmar and digital arterial occlusion and ischemic finger ulceration and gangrene was diagnosed in each patient. The associated diseases detected in these patients are listed in Table 3. The diagnosis of associated autoimmune disease was made by strict adherence to the criteria established by the American Rheumatism Association[21] and in routine consultation with the Division of Immunology at our University hospital. Autoimmune disease was diagnosed in 54% of the patients in this series. Digital artery occlusion caused by various autoimmune vasculitides is well described.[22]

Twenty-two patients had sudden onset of pain and distal finger cyanosis that rapidly progressed to ulceration or gangrene over 48–72 hours. Most of these patients were young (mean age: 36 years) and previously healthy; seven were female smokers taking oral contraceptives. All serologic tests for underlying autoimmune disease were negative both initially and during long-term clinical follow-up in this patient group. Fixed palmar and digital artery obstruction was documented by plethysmography and/or angiography in each patient. The acute ischemic event resolved with conservative treatment in every patient, and no recurrences have been observed with follow-up extending to 15 years. We reported the first ten patients with this condition in 1977 and termed it hypersensitivity angiitis with rapid onset vascular occlusion (ROVO).[23] Although our designation of this condition as hypersensitivity angiitis in the absence of tissue confirmation remains speculative, its similarity to the accepted hypersensitivity angiitides appears to us sufficiently close to warrant use of this classification.

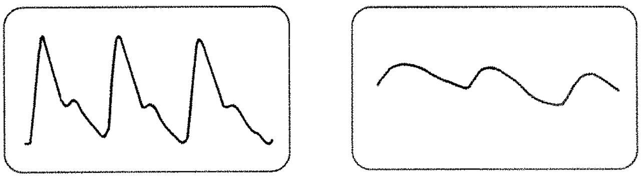


FIG. 1. *Left*, normal finger photoplethysmograph (PPG) showing normal upstroke and dicrotic notch. *Right*, PPG tracing in patient with finger ischemia demonstrating obstructive flattened waveform and absent dicrotic notch characteristic of digital artery obstruction.

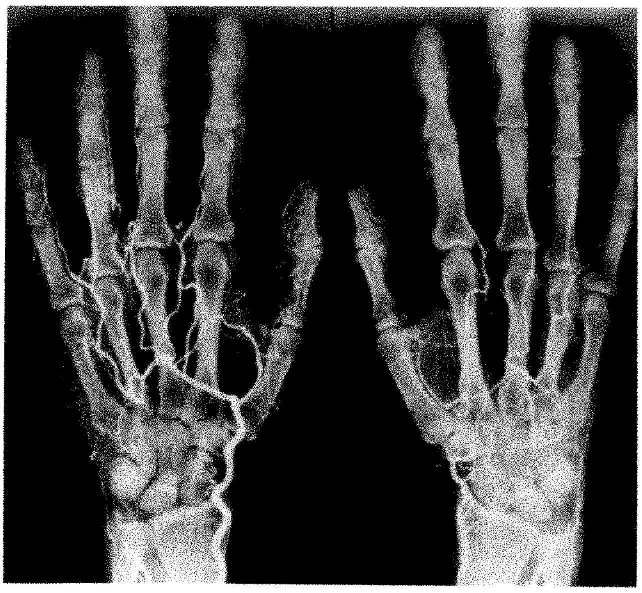


FIG. 2. Magnification hand arteriogram showing massive organic occlusion of the palmar and digital arteries with absence of complete filling of the superficial arch and occlusion of multiple proper digital arteries.

TABLE 3. *Underlying Diagnoses Established in 100 Consecutive Patients with Ischemic Finger Ulceration Caused by Small Artery Disease*

	N
Autoimmune disease	54
Scleroderma	17
CRST syndrome	8
Mixed connective tissue disease (MCTD)	5
Undifferentiated connective tissue disease (UCTD)	4
Rheumatoid arthritis (RA)	2
Systemic lupus erythematosis (SLE)	2
Sjogren's syndrome	1
Reiter's syndrome	1
Unclassified autoimmune disorder	5
Overlap syndromes	
RA, scleroderma	2
SLE, scleroderma	2
Sjogren's, scleroderma	2
Sjogren's, CRST	2
Dermatomyositis, scleroderma, CRST	1
Hypersensitivity angiitis (ROVO)	22
Thromboangiitis obliterans (Buerger's disease)	9
Atherosclerosis obliterans (ASO)	9
Malignancy	4
Lymphoma	1
Breast carcinoma	2
Renal cell carcinoma	1
Combined	2
ASO, CRST	1
ASO, scleroderma	1

Buerger's disease is a condition occurring predominantly in young male smokers. It is characterized by the occurrence of segmental occlusions of the small arteries in both the lower and upper extremities. Objective clinical criteria recently reported from our institution[24] were used to establish the diagnosis in nine patients in the current series. An additional nine patients had widespread large artery atherosclerosis that also involved the distal upper extremity and digital arteries as documented by arteriography. All of these patients, as well as those with Buerger's disease, were cigarette smokers.

TABLE 4. *Response of Ischemic Finger Ulceration to Conservative Treatment*

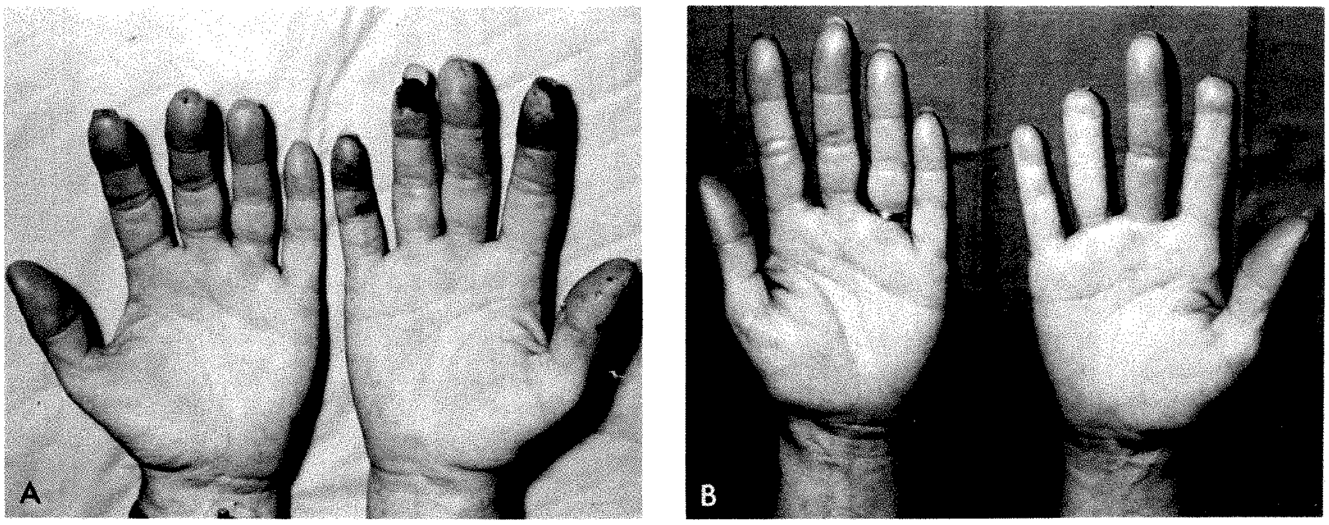
		N
Good Results 88%	Healing without recurrent ulceration	
	No residual symptoms	10
	Residual Raynaud's syndrome	52
	After minor debridement	10
	After conservative phalangeal amputation	16
Poor Results 12%	Recurrence of ulceration or amputation	
	Recurrent ulceration, tissue loss	11
	Hand amputation	1

An underlying diagnosis of malignancy was made in four patients with finger gangrene. Digital artery obstruction associated with malignancy has been described previously by us and others.[25,26]

Long-term Follow-up and Response to Therapy

All patients were treated using the conservative protocol described above. In addition to aggressive local treatment, numerous medications have been used over the past 15 years, both to treat patients in the acute phase of ischemia with active ulcerative lesions, as well as to treat subsequent Raynaud's syndrome, which occurred in 52% of patients after healing of the ischemic digital ulcerations.[27] The pharmacologic agents used included vasodilators, antiplatelet drugs, hemorrheologic agents, and immunosuppressive drugs directed at the active underlying autoimmune process (steroids, azathioprine, penicillamine). Early in our experience, we used Bier block or intra-arterial reserpine in 31 patients to achieve a regional sympathetic block,[28] followed by oral guanethidine and phenoxybenzamine. Symptomatic and angiographic improvement in vasospasm was documented in a number of patients for several days after parenteral treatment, but no consistent benefit was noted with long-term oral drug administration. We currently use a calcium channel blocker (nifedipine or diltiazem) alone or in combination with prazosin, with variable results. Currently, most patients also receive pentoxifylline. Although selected patients occasionally improve dramatically, the response to these drugs has not been predictable or reliable. We currently regard no vasoactive drugs of proven efficacy in the treatment of these patients.

Using the regimen described, with follow-up extending to 15 years (mean: 4 years), 88% of patients had complete healing without recurrent ulceration (Table 4). In 16 patients, a conservative mid-distal phalangeal amputation using a flap technique analogous to standard below-knee amputation was performed to relieve pain associated with unremitting distal finger ischemic pain. A representative photograph of ischemic digits before and after treatment is shown in Figure 3. In 12 patients, recurrent tissue loss or ulceration despite conservative care developed. Each of these patients had autoimmune disease, most frequently scleroderma (7 patients, Table 5). Cigarette smoking had no consistent relationship to outcome; although 68 patients in the series were smokers, only 20 successfully quit smoking. Half of the 12 patients with recurrent tissue loss had never smoked cigarettes. In contrast to those with autoimmune disease, patients with Buerger's disease, atherosclerosis (ASO), and hypersensitivity angiitis all did well and had



FIGS. 3A AND B. *A*. Initial presentation of a patient with gangrene of multiple fingers associated with hypersensitivity angiitis. *B*. Demonstrates complete healing after conservative treatment alone.

no recurrent finger ulceration or gangrene during follow-up.

Discussion

A careful analysis of the prospectively accumulated data in this group of 100 patients with advanced occlusive disease of the palmar and digital arteries associated with ischemic finger ulceration serves to establish the natural history of the condition. The occurrence of ischemic finger ulceration invariably signals the presence of a potentially serious associated disease. The methodical evaluation of these patients as outlined above has resulted in an accurate diagnosis in all, although careful long-term follow-up has been required to establish the diagnosis of associated disease in certain patients. The majority of these patients (54%) had an underlying autoimmune disorder. Optimal patient management required participation by a rheumatologist or immunologist to coordinate systemic treatment regimens. Our simple conservative local finger treatment program of vigorous local cleansing with plain soap and water with minimal debridement of necrotic and infected tissue, accompanied by the administration of culture-specific antibiotics, was followed by healing without recurrent tissue loss or ulceration in 88% of patients with follow-up to 15 years.

Other investigators have published healing rates for other forms of treatment of upper extremity digital gangrene. A 75% healing rate followed treatment with intravenous prostaglandin E1 infusion.[29] Similar rates of healing have been attributed to the performance of cervicothoracic sympathectomy.[7,30] These results clearly are no better than the 88% permanent healing rate without recurrence reported in the current series with conservative treatment only. We performed no thoracic sympathectomies in these patients, although 11 patients had had sympathectomy, all without benefit, before referral to our center. We find no evidence that regional sympathectomy is of any demonstrable benefit either in accelerating initial healing or in controlling chronic, persistent vasospasm, when associated with arterial obstruction.

Hypersensitivity angiitis (ROVO) is an especially interesting condition. Its clinical course resembles an immune vasculitis with distribution limited to the small arteries of the hand. Interestingly, there appears to be no systemic toxicity. None of the 22 patients in the current report who had this condition experienced a recurrence, often despite the persistence of risk factors such as cigarette smoking. Long-term improvement was associated with the development of collateral arterial circulation, as

TABLE 5. *Underlying Diagnoses in Patients with Recurrent Ulceration and Tissue Loss*

	N
Scleroderma	5
Mixed connective tissue disease	2
Undifferentiated connective tissue disease	1
CRST syndrome	1
Overlap/combined syndrome	
Sjogrens, scleroderma	1
Scleroderma, ASO	1
Dermatomyositis, CRST	2
Total	12 (12%)

the initial major digital artery obstruction invariably persisted as documented by serial photoplethysmography and repeat arteriography in several patients.

As noted above, we have used a variety of vasoactive medications in these patients directed at improving circulation through relief of associated vasospasm. We are unconvinced that any of these drugs have been of benefit in healing the digital ischemic ulceration, although occasionally they have appeared helpful in the symptomatic treatment of obstructive Raynaud's syndrome, which frequently follows the episode of ischemic ulceration. Our recent anecdotal experience with the hemorrheologic agent pentoxifylline has been encouraging in a small number of patients with ischemic ulceration, although to date no controlled study has been performed.

Our opinion concerning the requirement for arteriography in the evaluation of these patients has changed over the years. Until recently, all patients with ischemic finger ulceration had arteriography to document digital artery occlusion and to rule out a proximal embolic source. We currently believe that if finger gangrene occurs in a patient in whom a firm diagnosis of associated disease has been established and in whom digital photoplethysmography is diffusely abnormal bilaterally, arteriography is unnecessary. If no diagnosis has been established, and particularly if symptoms and signs are unilateral, angiography from the aortic arch to the fingertips should be performed to detect surgically correctible proximal large artery lesions that may be responsible for the digital ischemia.

During this 15-year period while we evaluated and treated 100 patients with finger gangrene caused by small artery disease, we encountered only six patients with finger gangrene caused by large artery disease, most frequently giant cell arteritis with involvement of the axillary artery.[31] Certainly in our experience, proximal large artery disease of the upper extremity is far less likely than palmar and digital small artery occlusive disease to cause profound finger ischemia with ischemic ulceration. It is unknown whether this reflects the relative incidence of these two conditions in the population or pecularities of our local referral pattern.

The results of this review indicate that the occurrence of ischemic finger ulceration invariably heralds the presence of a potentially serious underlying disease process and that methodical evaluation of these patients should result in an accurate diagnosis. The natural history of ischemic finger ulceration in 88% of our patients has been long-term healing without recurrence after conservative treatment. We are unconvinced that any therapy improves on vigorous local cleansing, debridement, antibiotics, and conservative amputation/debridement. We find no evidence that thoracic sympathectomy or vasodilator drug therapy significantly benefits these patients.

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Discussion

DR. HENRY T. BAHNSON (Pittsburgh, Pennsylvania): I presume there was no frost bite or did you exclude frost bite in that group of patients?

DR. HERBERT I. MACHLEDER (Los Angeles, California): Over the past several years, Dr. Porter and his co-workers have presented a series of valuable observations documenting many characteristics of upper extremity digital ischemia. The combination of their unique therapeutic approach and excellent results have encouraged us to critically review our own management of these patients.

It has become evident to me that even in this large series of patients, there are some hazards in drawing generalized conclusions from one facet of such a disparate group of diseases. For example, in our experience at UCLA, patients with hypersensitivity vasculitis and those with leukocytoclastic vasculitis have a self-limited course that seems to be dependent on exposure to environmental or endogenous allergens. The disease process is related to removal or persistence of this allergen, which can be either a chemical, medication, pharmacologic agent, or a mycotic or bacterial infection. Once this event is controlled, the vasculitis usually regresses and rarely returns. In this self-limited type of disease, long-term pharmacologic therapy or sympathectomy is clearly irrelevant.

On the other hand, connective tissue and autoimmune vasculitic disorders are characterized by exacerbations and remissions, which usually require a long-term commitment to therapy. We have studied a group of 20 of our most severely ill patients, with severe systemic autoimmune disease, using long-term thoracic duct drainage as an immunosuppressive agent.

Evidence of vasculitis begins to resolve rapidly after the onset of immunosuppression. Within 3 weeks there is no longer any clinical evidence of the vasculitic lesions or digital ischemia. Usually within 2–3 months, vasculitis can no longer be demonstrated by biopsy of previous lesions. Dermal-epidermal junctions or vascular endothelium no longer show deposition of IGG and beta-1-C or immune complexes.

Clearly in this group of patients digital ischemia is a barometer of the underlying systemic disease and cannot be viewed as an isolated phenomenon. Our approach therefore has been to direct therapy towards the underlying disease process. I wonder if the excellent results achieved by the group in Oregon can be attributed to control of the underlying autoimmune or collagen vascular disease rather than the specific measures directed at the secondary manifestations.

Another example would be polyarteritis, which is very sensitive to immunosuppressive therapy. A large group of these patients have been studied by a randomized controlled trial and have demonstrated that the addition of Imuran® to the usual prednisone regimen can significantly change the outlook for these patients. Mean survival can be augmented from 5 years to 12 years and the 5-year survival rate can be changed from 50% to 80%.

Management of digital ischemia, then, in our institution, has been subordinate to the systemic therapy, which is probably the most important factor influencing the course of digital gangrene. Nevertheless, we have been considerably more liberal in our use of sympathectomy and pharmacologic therapy, as a palliative measure, than indicated in this current series.

Dr. Wiley Barker and I reported our results with 53 patients, 81% of whom were relieved of their symptoms. These results from sympathectomy are comparable, but not quite as good as Dr. Porter's 85–88% remission.

We have found that a number of additional symptoms, such as Raynaud's phenomenon, digital hypersensitivity to cold, and digital hypersensitivity to touch, precede frank ulceration and often continue after healing. These symptoms can be favorably influenced by a more aggressive therapeutic approach, and may reduce what is often considerable physical and occupational disability.

I have two questions for the authors: how did you treat the 12% of patients who failed the conservative management program? The second question is: nonrecurrence of digital ischemia in Buerger's and scleroderma is certainly very unusual in our experience. This suggests much better control of the underlying disease process than we have been able to manage. What is your primary approach to therapy then in these difficult autoimmune diseases?

PROFESSOR JAN NIELUBOWICZ (Warsaw, Poland): I want to save the time for Poland. I am a general and vascular surgeon, and have been very much interested in this question that has been presented.

I congratulate the authors for their very nice and interesting presentations, and I want to make some comments concerning the nonhealing ulcers in Buerger's disease and in Raynaud's phenomenon.

I have studied these patients very much, and as you know, everybody thinks that Poland is the native country for Buerger's disease, which is not true because you find it everywhere in the world.

I made a study of about 120 patients whom I gathered during the years of my work in Warsaw. I published and presented it at the international meeting in Tokyo some 8 years ago, and that has been published in the *Journal of Cardiovascular Surgery.* I have two remarks, I believe, that all these patients get Buerger's disease, which is proved by histopathologic studies, in the course of 4 or 5 years, and 80 or 85% lose their fingers.

The second remark that I want to make is that interestingly enough, when all fingers of the extremities are amputated, their natural course of life is just the same as anybody's life. What Dr. Bahnson is showing to me, 99% of them are heavy smokers. Then the next comment that I want to make if on Raynaud's phenomenon, which frankly speaking, people have not worked on since Raynaud's original description. We do not know the mechanism of this pain during the cyanotic phase of Raynaud's phenomenon. I proved that the pain phase is due to the opening of the natural arterial venous communications. This makes the periphery ischemic. In Raynaud's phenomenon, we do the sympathectomy only in cases of severe pain.

I agree with the speakers that although the pain disappears or diminishes, it reappears after 6 months; therefore, the indications for that type of operation are very limited.

DR. FRANK COLE SPENCER (New York, New York): I rise primarily to comment briefly and ask two questions.

This is a remarkable follow-up for which we are all indebted for what is one of the most careful, long-term studies of an unusual disease in the world. It well demonstrates the need for randomization of different forms of therapy, especially with long-term chronic diseases.

Concerning etiology, about 75% of the patients were considered to have an autoimmune disease, 50% were considered to have a clear autoimmune disorder, and 25% were considered to have "hypersensitivity angiitis." There were only four patients with a malignancy.

The vascular episodes in both groups appeared to be acute ischemic episodes, resulting from an embolus or a trombosis. There were acute symptoms with tissue necrosis, subsiding with simply soap and water wound care; yet the disease did not recur. The recovery with simple wound care, I suppose, is due to both lack of progression of the underlying disease as well as the growth of collateral circulation.

Hence, the major question is: what is the basic disease? Why didn't it recur? Certainly the ischemic phenomena are similar to those with Buerger's disease, which is notorious for its recurrence and chronicity.

My other question relates to the descriptive term "hypersensitive angiitis." Is this an established entity or primarily an adjective that describes a syndrome in someone who has immunologic findings of an autoimmune disease but not other abnormalities that permit a precise diagnosis?

DR. MORTON M. WOOLLEY (Los Angeles, California): Infants and children with scleroderma are not infrequently seen because of painful subcutaneous abcesses. The abscess generally occurs around a central calcium deposit. I would like to ask the authors if the adult patients described in their manuscript have an underlying collection of calcium in association with the cutaneous ulcerations.

DR. ISRAEL PENN (Cincinnati, Ohio): I would like to comment on another autoimmune disease, namely diabetes mellitus. Kidney transplantation has significantly prolonged the lives of many patients with juvenile onset diabetes who have chronic renal failure. Unfortunately, the metabolic disturbances persist and many patients get progressive vascular disease. Virtually every transplant surgeon has had the disappointing experience of having to perform a significant number of lower extremity amputations in these individuals. In addition, there are occasional patients who also have small vessel disease involving the palmar and digital vessels and present with painful ischemic ulcers of the fingers. Unfortunately, these lesions do not respond to conservative treatment and the patients end up with multiple amputations of their fingers.

I would appreciate if you would describe your experience with diabetic patients.

DR. JOHN M. PORTER (Closing discussion): As you can all tell from the presented material the objective of the study was descriptive. Before making the observations reported herein, we did not know the natural history of ischemic finger ulcerations nor did we know the associated disease processes routinely present in these patients.

Dr. Machleder and I have shared an interest over the years in small artery disease, especially of the upper extremity. He observed accurately that hypersensitivity angiitis might normally end when the offending antigen is removed. Although true, we frequently do not know the identity of the offending antigen.

We did not identify specific chemical toxins in our patients, and, as noted in the manuscript, our use of the term "hypersensitivity angiitis" is speculative. The arteritis which we hypothesize bears only remote resemblance to either leucocytoclastic angiitis or hypersensitivity angiitis of Zeek.

The immunology group at UCLA has been among the leaders in the definition and treatment of autoimmune disease, and Dr. Machleder's comments directed towards specific immune therapy including lymph duct drainage are most interesting. We did not embark on a specific therapeutic program such as this, and I have no further comments in that area. His observation that the Raynaud's syndrome if frequently improved by sympathectomy is in my opinion partially true but generally irrelevant.

I find that one can accurately categorize the Raynaud's syndrome into two specific categories: obstructive and spastic, with careful adherence to a variety of vascular laboratory and serologic testing. Patients with spastic Raynaud's syndrome will frequently respond well to sympathectomy. In the main, however, they do not require such extreme therapy. Patients with obstructive Raynaud's syndrome respond poorly to sympathectomy and I believe it is generally contraindicated in this group.

Dr. Machleder asked how we treated the 12% of patients who failed. We had no specific therapy in these patients other than finger debridements and local wound care.

I observe that we do not recommend and have never used proximal finger amputation as initial therapy. If one performs finger amputation through the proximal or midphalanyx, primary healing can be achieved in almost 100% of patients, but at the expense of sacrifice of finger length. As conservation of finger length is so important for hand function, we performed fingertip conservative resectional debridement in the majority of these patients in an effort to preserve maximal length.

Professor Nielubowicz' comments are appreciated concerning the progression of Buerger's disease. Our patients with Buerger's disease whom we have recently reviewed have almost all displayed progression of disease in relationship to cigarette smoking. I personally had doubts about this relationship until our recent review, which again validated these historic observations.

Any benefit in the healing of ischemic fingertip ulceration from thoracic sympathectomy in my opinion remains completely anecdotal. Without question, if one performs a sympathectomy in the course of a program of treatment for fingertip ischemic ulceration including debridement antibiotics, and scrubs, the ulcers will heal in about 85% of patients. Our contention is that the same treatment program without the thoracic sympathectomy will produce identical results.

Dr. Spencer perceptively asks why the ischemic finger ulcers did not recur since our treatment was only supportive and nonspecific. I believe this is the most fascinating observation in this patient group. One would expect if the patient has serious underlying small artery disease, sufficiently severe to cause finger ulcer, and all we offer if local treatment, the ulcer should recur within weeks or months. Interestingly, in 88% of our patients, this did not happen. I report this as an observation on the natural history of this disease for which I have no explanation. I do believe that any future study evaluating various therapeutic regimens must be measured against the natural history of the condition as presented herein. I believe that is the most important observation we have made to date.

Dr. Woolley, we did find finger calcification in certain patients, although I observe that the finger calcifications were more of the diffuse variety. We did not find the very localized calcium deposits that sometimes occur.

Interestingly, only 9% of this patient population had diabetes. We have a large group of diabetic patients in our clinical series. In fact, in our peripheral arterial bypass series, about 55% of our patients are diabetics. I have no explanation for the small number of diabetics in the ischemic finger ulceration group.

Splenectomy for Primary and Recurrent Immune Thrombocytopenic Purpura (ITP)

Current Criteria for Patient Selection and Results

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Of 565 patients with thrombocytopenia admitted to Duke University Hospital between 1975 and 1985, 100 had splenectomy. Ninety-eight patients had failed chronic immunosuppressive therapy and three patients had acute intracranial bleeding or total absence of platelets in the peripheral blood smear, and had urgent splenectomy. At primary splenectomy, accessory spleens were identified and resected in 18% of patients. There was no operative mortality. Fifty-eight patients had an excellent response to splenectomy and their steroids were tapered off within 3 weeks. Thirteen patients had a poor response to primary splenectomy of whom eight remitted spontaneously and five required accessory splenectomy resulting in complete remission in three patients. Twenty-nine patients were considered nonresponders, 25 of whom had radionuclide scanning for accessory spleens. Seven of these patients had accessory spleens identified but only four consented to accessory splenectomy. In three of the four patients, a complete remission was achieved. Neither platelet antibody titers nor measurements of platelet survival or turnover predicted platelet response to splenectomy. However, immune thrombocytopenic purpura (ITP) in older patients was significantly less likely to respond to splenectomy. These data support continuing use of splenectomy in selected patients with ITP and an aggressive search for accessory spleens in patients who relapse since they are easily localized at operation by hand-held isotope detector probe.

THE DEMONSTRATION IN 1913 that splenectomy benefited some patients with hemolytic anemia led Kaznelsón to advocate its use for the treatment of "purpura haemorrhagica" in 1916.[1] By 1926, Whipple[2] could identify 81 patients in the literature who had had splenectomy for immune thrombocytopenic purpura (ITP). Reports of successful cases by Spence[3] in 1928, and by Eliason and Ferguson[4] in 1932, brought the collected experience to 213 patients, and established splenectomy as the only definitive therapeutic procedure for ITP. Although this new mode of therapy became rapidly accepted, the mechanism responsible for the low platelet count in ITP and the efficacy of splenectomy in some of the patients were poorly understood. The leading hypothesis included a decrease in the rate of platelet formation from megakaryocytes because of splenic inhibition of these cells. Others believed that there was an increase in the rate of platelet destruction by the spleen.

An immune mechanism was first suggested by Marino[5] in 1905. Marino produced an antiplatelet antibody by injecting rabbit platelets into guinea pigs. A few years later, Ledingham[6] caused experimental purpura in animals by the administration of antiplatelet antiserums. However, little extension of these fundamental studies into clinical states of thrombocytopenia was made until in 1938, when Evans et al.[7] presented evidence of a thrombocyte agglutinating factor in the serum of patients with ITP. Their theory that a circulating antibody was responsible for the thrombocytopenia of ITP was later proved by Harrington et al.[8] by cross-transfusion between purpuric and normal volunteers. The relationship between circulating antibodies and splenectomy was dramatically established 2 years later by Harrington,[9] who showed that the thrombocytopenic effect on normal recipients given plasma from subjects with ITP was diminished in the absence of a spleen.

It was about this time that glucocorticoids were first demonstrated to be effective in the treatment of ITP.[10] With the introduction of even more powerful immuno-

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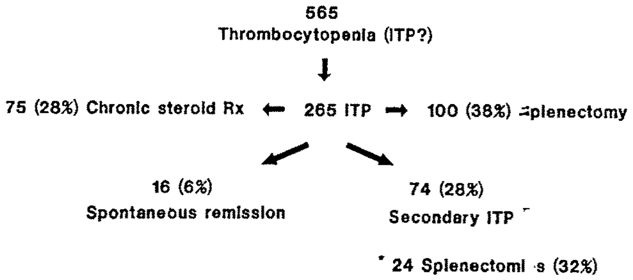

FIG. 1. One hundred patients with primary ITP had splenectomy. Twenty-four patients believed to have primary ITP had splenectomy, but in whom other diseases subsequently developed, were not included in the current study.

suppressive agents, such as azathioprine, cyclophosphamide, and the vinca akaloids, splenectomy was gradually relegated to a secondary role. Recently, hyperimmune globulin has also been demonstrated to be effective in restoring thrombocytosis, albeit transient, in selected patients with chronic ITP.

To assess the impact of this apparently changing role of splenectomy on our practice, we reviewed the experience at Duke University Medical Center. Our specific aim was to document our criteria of patient selection for splenectomy and to analyze the current results.

Materials and Methods

Patients

Between 1975 and 1985, 565 consecutive patients with thrombocytopenia of obscure cause were referred to the Hematology Section at Duke University Medical Center for evaluation and management (Fig. 1). Two hundred sixty-five of these patients satisfied the diagnostic criteria of ITP. In 16 (16%) of these 265 patients, the thrombocytopenic state remitted during a very short period of observation or treatment with low doses of steroids. These 16 patients were young, with an average age of 9 years. Seventy patients (28%) had sustained platelet responses on chronic therapy with steroids and were managed medically. Seventy-four patients (28%) who initially were believed to have primary ITP subsequently developed other diseases. Twenty-four patients in this group had had splenectomy before the onset of the secondary disease.

The remaining 100 patients (38%) identified as having primary ITP were the focus of this study. After evaluating the impact of splenectomy, each patient could be categorized as a *responder* or a *nonresponder*. Response was defined strictly by the patient's ability to sustain a platelet count (measured by the Duke Special Hematology Laboratory) of greater than 150,000/μL after primary and/or accessory splenectomy, and on no medical therapy during the follow-up period. Nonresponders failed to respond to primary and/or accessory splenectomy or relapsed after an initial response. Nonresponders required chronic immunosuppressive therapy to prevent their platelet counts from plunging into dangerously low levels.

Platelet Counts and Platelet Antibody Titers

Platelet antibody titer measurements were paired with their corresponding platelet counts, before and after splenectomy.

Before 1981, the platelet antibody titers were determined by a complement lysis inhibition assay using rabbit antihuman IgG. Since 1981, the antibody titers have been measured by a specific radioimmunoassay using a platelet radioactive antiglobulin test.

For the purpose of our analysis, the platelet antibody titers were standardized by dividing each measured value by the corresponding normal value for the technique of antibody measurement by which it was determined. Among the *responders,* 95 observations were made before splenectomy and 126 were made after operation. Fifty-eight presplenectomy and 123 postoperative observations were recorded in *nonresponders.* Platelet antibody titers in patients with accessory spleens were considered only when the measurements were made before primary splenectomy (preoperative titer) and again after accessory splenectomy (postsplenectomy titer).

The data were then normalized by taking the logarithmic transformation of both the standardized platelet antibody titer and of the corresponding platelet count. The partial correlation and regression coefficients between these two variables were then calculated for each category before and after splenectomy, blocking on individuals for whom there were multiple observations. The probability associated with testing each coefficient against the null hypothesis was calculated using the z-statistic for the partial correlation coefficients and the t-statistic for the regression coefficients. A chi-square test using Fisher's transformation was used to test the equality of the partial correlation coefficients, and the z-statistic was used to test the equality of the regression coefficients.

Platelet Survival and Platelet Turnover

Platelet survival and turnover were determined using autologous platelets labelled with indium III oxyquinoline. The platelet separation and labeling were performed according to techniques originally described by Thakur et al.[11] Blood samples are obtained at 15 minutes, 1 hour, 2 hours, 4 hours, and daily after injection of the radiolabeled autologous platelets. Two milliliters of whole blood from each sample and a standard of the injectate are counted on the last day of sample collection in an automatic scintillation well counter. Survival is calculated using a computer program that uses the gamma function (multiple hit) model.[12] The recovery of labeled platelets in the circulation is calculated from the activity per milliliter of each sample and from the estimated blood volume.

The platelet turnover was calculated by a standard formula:[13]

$$\text{platelets}/\mu\text{L/h} = \frac{\text{platelet count } (\mu\text{L}) \times 90\%}{\text{life span (hours)} \times \text{initial recovery}}$$

where the 90% figure represents the percentage of platelet recovery in normal subjects without spleens.

Eighteen patients had platelet survival studies, in 12 of whom the initial recovery was available for calculation of platelet turnover. The Pearson Product moment correlation coefficient was then calculated between both the logarithmic transformation of both platelet survival and turnover and the log transformation of the platelet count at 6 weeks after splenectomy. The probability associated with testing each coefficient against the null hypothesis of no linear relationship was then calculated.

Radionuclide Imaging of Accessory Spleens and their Intraoperative Localization Using a Hand-held Isotope Detector Probe

Eleven patients in whom ITP was refractory to primary splenectomy had conventional liver spleen scintigraphy with technitium 99 sulfur colloid to include anterior, posterior, lateral, anterior oblique, and posterior oblique images. If no splenic tissue is identified, a posterior image with increased intensity is performed to determine if a small amount of splenic tissue is present that is not detectable on the routine images. With the introduction of indium 111-labeled autologous platelets in 1981 at Duke University Medical Center, 19 of our patients with no response to splenectomy had an indium 111 radionuclide study. After injection of the radiolabeled autologous platelets, images are obtained with a wide field of view scintillation camera (Siemens LFDV, Siemens Medical Systems, Inc., Iselin, NJ) equipped with a medium energy parallel hole collimator. Symmetric 20% windows around the 173 Kev and 247 Kev photopeaks of indium 111 are used. Anterior, posterior, and left lateral views of the abdomen are obtained.

If an accessory spleen is detected, the patient is taken to the operating room within 12 hours of the radiolabeled platelet injection. A hand-held isotope detector probe is used for intraoperative localization of accessory spleens. The active detector, a cylindrical crystal of thallium-activated sodium iodide, detects gamma photon energies up to 160 Kev, is coupled to a photomultiplier by a light-pipe combination consisting of an inactive sodium iodide crystal and an acrylic coupler section. The active detector, photomultiplier, and electrical networks necessary in connecting the two are contained within a lead shield. Two 20-foot cables, one for high voltage and one for signal, connect the probe to its associated electronics. The probe is gas sterilized and used intra-abdominally during surgery to detect accumulation of indium 111-labeled platelets at the site revealed by the scan. The focus is removed and demonstrated *ex vivo* to have increased activity, whereas activity at the focus site is demonstrated to have returned to background levels. Finally, immediate pathologic confirmation of splenic tissue is obtained by submitting the resected specimens for frozen section examination.

TABLE 1. *Presentation of Immune Thrombocytopenic Purpura, Duke University 1975–1985*

Sign	Percentage of Patients (N = 100)
Easy bruising only	28
Routine platelet count	17
Petechiae, purpura, ecchymosis	14
Bleeding (gum, epistaxis, gastrointestinal, genitourinary)*	41

* Two patients with intracranial hemorrhage had urgent splenectomy.

Results

Demographic

There were 58 females and 42 males with an overall average of 41.4 years (range: 5–84 years). The ratio of blacks to whites was 1 to 4.

Presentation Diagnosis

A history of viral illness could be elicited from 19 patients. Seven patients received diazide, three patients received quinidine, and one patient gave a history of exposure to industrial solvents. The remaining patients had no recent infection or drug exposure that could be implicated in their thrombocytopenic state.

Abnormal bleeding was the most common sign of ITP, occurring in 41% of patients (Table 1).

Easy bruisability occurred in 28% and was associated with purpura, ecchymosis, or petechiae in 14 patients (14%).

In 17% of patients, the diagnosis was uncovered when an incidental complete blood count showed low levels of platelets (Table 1).

In addition to their clinical presentation, the diagnosis of primary ITP was supported by the absence of spleno-

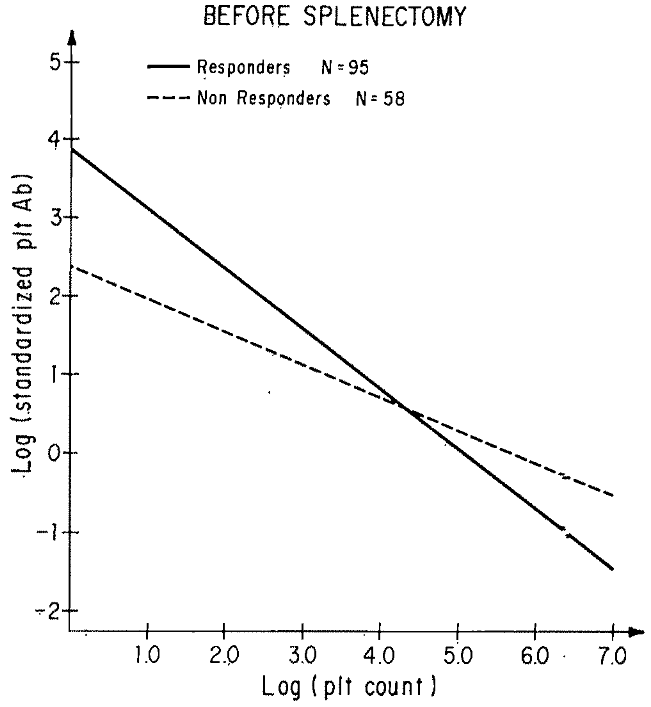

FIG. 2A. Regression lines between log (standardized platelet antibody titer) and log (platelet count) before splenectomy. Although the inverse relationship between these two variables is strongly negative ($p < 0.05$), there was no difference between responders and nonresponders ($p > 0.05$).

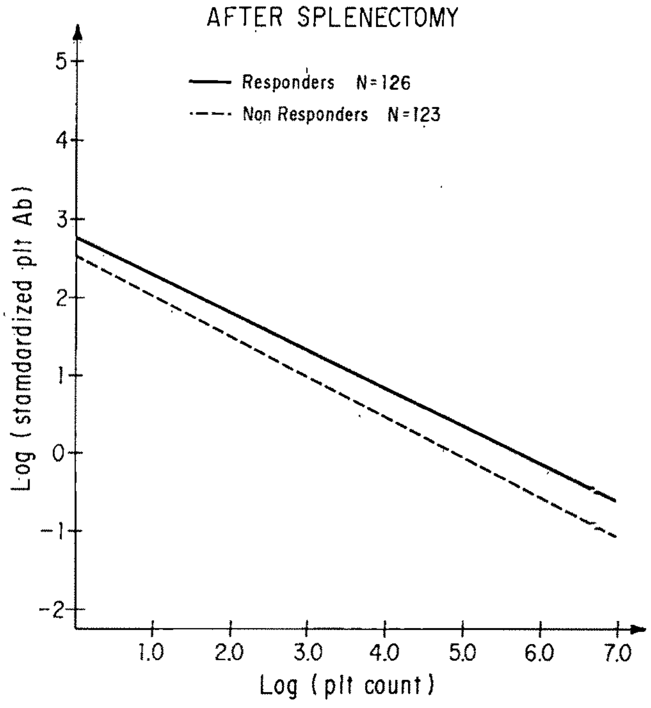

FIG. 2B. Regression lines between log (standardized platelet antibody titer) and log platelet count after splenectomy. Slopes of regression lines remain strongly negative ($p < 0.05$) and are not different from the preoperative values. After splenectomy, the slope of the regression lines are identical between responders and nonresponders.

megaly on physical examination and scintigraphic scans, low platelet counts associated with abnormally high titers of antiplatelet antibody, a bone marrow aspirate showing normal or increased number of megakaryocytes with decreased platelet budding, and normal maturation of the erythrocytic and granulocytic cell lines. Serologic tests were consistently negative for connective tissue disorders in all patients throughout the follow-up period (26–120 months).

Platelet Count and Platelet Antibody Titers

The overall average platelet count of the patients at presentation was 21,000/μL. The regression coefficients relating log platelet count and their corresponding log platelet antibody titers were negative in both responders (−0.77 ± 0.14) and nonresponders (−0.38 ± 0.18) before splenectomy (Fig. 2A). Although these coefficients were not different from each other ($p = 0.09$), they were significantly negative when individually tested against the null hypothesis ($p < 0.05$) (Figs. 2A and 2B).

Before splenectomy, the partial correlation coefficient between log platelet count and log platelet antibody titer for responders was −0.50 and was −0.31 for the nonresponders (Fig. 3). The difference between the two was significant ($p = 0.05$).

Platelet Survival and Platelet Turnover

Platelet survival, which is normally 200–220 hours, was shortened to an average of 61.5 hours in the 34 patients in whom it was measured. Average platelet turnover increased in 2179 platelets/μL/h (N = 1200–1600 platelets/μL/h) in 12 patients in whom it was calculated.

Initial Therapy

All patients represented failures of chronic nonoperative therapy, except for three patients who had urgent splenectomy (Table 2). Emergency splenectomy was advised in two patients with acute intracranial bleeding and in one patient who showed a total absence of platelets in repeated peripheral blood smears.

The average time from presentation and institution of medical therapy to primary splenectomy was 8 months (range: 0.5–96 months) (Table 2).

Fifty-one per cent of patients were unresponsive to prednisone at doses in excess of 60 mg/day. In 35 patients, prednisone was used in combination with other immunosuppressives (vincristine, cytoxan, or azathioprine), either because of the patient's inability to tolerate prednisone in high doses or because the prednisone dosage could not be tapered to lower levels without the platelet count dropping to clinically unacceptable low levels.

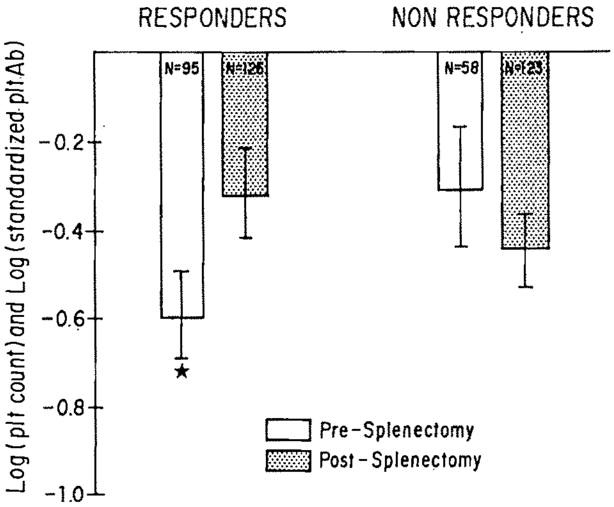

FIG. 3. The partial correlation coefficient between log (platelet count) and log (platelet antibody titer) in the responders before splenectomy was significantly higher (*$p < 0.05$) than in all other categories. The partial correlation coefficient between these two variables was not different in the nonresponders before and after splenectomy ($p > 0.05$).

Eleven per cent of patients had a good response to prednisone in the 20–60 mg/day dose range but unfortunately had severe side effects of steroid therapy or adverse effects of steroids on the patients' other coexisting medical conditions.

Although patients who ultimately responded well to splenectomy had been treated medically on average for a shorter time than had the nonresponders (7 months *vs.* 12 months), this difference is probably due to physicians' reluctance to refer older patients for surgical therapy (Table 2, Fig. 4).

Primary Splenectomy

All 100 patients received preoperative pneumococcal vaccination as well as steroid preparation. In general, the patients received 100 mg of hydrocortisone on the day before operation and approximately 300 mg of hydrocortisone on the day of surgery and the immediate postoperative period. The dosage of steroids was then gradually reduced depending on the patient's platelet response.

In an effort to investigate the possible role of preoperative infusions of intravenous gamma globulin for establishing preoperative thrombocytosis and thus obviate the need for platelet transfusions, we studied six patients. Four patients received 400 mg/kg/day of gamma globulin (IV-IG) on each of 5 days. Shortening the protocol, two patients were given 1000 mg/kg/day for 2 days. All six patients achieved platelet counts in excess of 100,000/μL and did not require perioperative platelet transfusion.

TABLE 2. *Therapy Before Primary Splenectomy, Duke University 1975–1985*

	Therapy No. of Patients				Duration (Months)
	$\bar{S}$	S + I	S	N	Average (Range)
Responders	39	19	10	3†	7* (0.5–96)
Nonresponders	12	16	1	0	12 (1–74)
Total	51	35	11	3	8 (0.5–96)

* Significantly shorter than in nonresponders. ($p < 0.05$)
† Underwent urgent splenectomy.
$\bar{S}$ = High-dose prednisone (50 mg) with poor response.
S + I = 20–40 mg of prednisone/day and one other form of immunotherapy with poor response.
S = 20–60 mg of prednisone/day with good response but intolerance.
N = No medical therapy before splenectomy.

Fifty-one patients with an average platelet count of 45,000/μL were given platelet transfusions during operation. The remaining 43 patients had an average preoperative platelet count of 83,000/μL on steroids and did not receive platelet transfusions.

The tail of the pancreas was protected during operation and every effort made to remove the spleen intact to avoid the liberation of fragments resulting in splenosis. Careful examination of the gastrocolic omentum, the retroperitoneum along the splenic vessels especially near the hilum, the bowel mesenteries, and the pelvis in the female patients, was performed in all cases. Eighteen patients (18%) had one or multiple accessory spleens at the time of primary splenectomy. Thirteen (72%) of

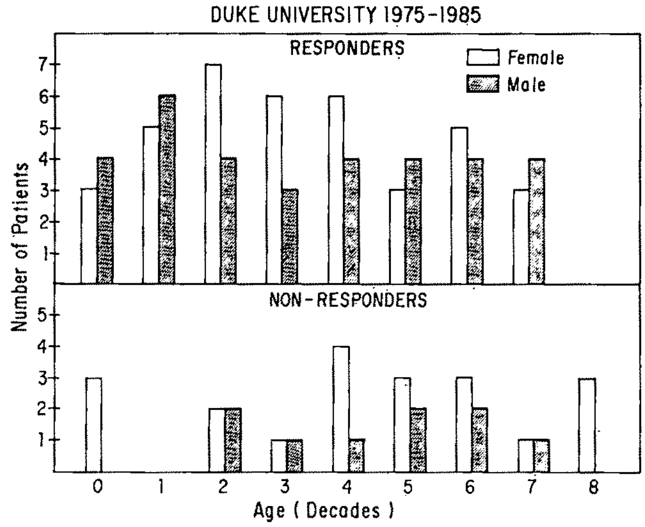

FIG. 4. Age and sex distribution in 100 patients who had splenectomy for ITP. The nonresponders (mean age: 49.3 ± 4.3) were significantly older than the responders (mean age: 38.2 ± 2.5; $p < 0.05$). The nonresponders were predominantly female but the gender differences did not achieve statistical significance ($p > 0.05$).

these accessory spleens were found in patients under 40 years of age.

The average weight of the spleen was 147 g (range: 39–340 g) and no distinctive alterations of their gross architecture were found. Histologic examination revealed an increased number of secondary follicles with large and active center in about 50% of patients. Sinusoidal dilatation in the red pulp was present in most patients.

Outcome after Primary Splenectomy

Seventy-one patients had a good response to splenectomy achieving a platelet count above 150,000/μL while receiving no medication. There were 38 females and 33 males with a mean ± SEM age of 38.2 ± 2.5 years (Fig. 4). Of these patients, 58 had an excellent response to primary splenectomy over a mean follow-up period of 10 months (range: 1–61 months); their steroid regimen was tapered within the first week after operation and they were completely off steroids an average of 2.3 weeks after operation. Another 13 patients had an initial poor response to primary splenectomy; eight remitted spontaneously during medical therapy for an average of 34 months (range: 1–84 months) after primary splenectomy and five had accessory splenectomy with good result in three of these patients who have required no further treatment.

After splenectomy the regression coefficient between the log platelet count and their corresponding log platelet antibody titers for these responders was −0.48 ± 0.15 and was not different from the presplenectomy coefficient of −0.77 ± 0.14 ($p = 0.17$) (Figs. 2A and 2B). However, the partial correlation coefficient was −0.32 and was significantly different from the presplenectomy value of −0.60 ($p < 0.05$) (Fig. 3).

Twenty-nine patients (29%) were considered nonresponders to primary splenectomy, and continued to require immunosuppressive therapy to maintain their platelet counts above dangerous levels. Included among the 29 patients were four patients who initially had a good response to primary splenectomy and subsequently had relapse of ITP, and three patients who required accessory splenectomy with no subsequent response. In these nonresponders, the regression coefficient of 0.38 ± 0.18 ($p = 0.45$) (Figs. 2A and 2B). The partial correlation coefficient for the nonresponders after splenectomy (−0.31) was not different from the presplenectomy coefficient (−0.45, $p = 0.37$) (Fig. 3).

The nonresponders were significantly older than the responders and although they were predominantly female, the gender differences did not achieve statistical significance (Fig. 4).

The Pearson correlation coefficient between the log preoperative platelet survival or turnover and the log postoperative platelet count were 0.017 and 0.33, respectively, which are not statistically significant ($p > 0.05$). Thus, neither platelet survival nor turnover predicted postoperative response of platelet count in these patients.

There was no operative mortality. Two patients who had recovered completely from operation died 3 months after operation, one of generalized sepsis and the second of multiple pulmonary emboli. The operative morbidity rate was 8%, consisting of three patients with subphrenic abscesses (one requiring drainage), one case of upper gastrointestinal bleeding that stopped after the saline lavage, two cases of multiple pulmonary emboli, and one case each of generalized sepsis and perirectal herpes simplex. Both patients with intracranial bleeding recovered completely.

Accessory Splenectomy for Persistent or Recurrent ITP

Of the 29 patients classified as nonresponders, 25 patients had a total of 30 radionuclide imaging studies. Six patients had only a technitium 99m sulfur colloid scan, which identified accessory spleens in three patients. Fourteen patients had only an indium 111-labeled platelet scan, revealing accessory spleens in eight patients. Both types of imaging were used in five patients. The presence of an accessory spleen was questioned on the Tc 99m scan in one patient but was very clearly imaged by the indium 111 scan. A second patient who had an accessory spleen identified by technitium 99m sulfur colloid scan was operated on but had persistent thrombocytopenia after excision of the accessory spleen. An indium 111 scan was performed that identified a second accessory spleen. The patient's ITP remitted completely after the second accessory splenectomy.

Accessory splenectomy for recurrent (5 patients) or persistent (4 patients) ITP was done in nine patients (Table 3). The average interval between primary and accessory splenectomy was 168 months (range: 1–504 months). The accessory splenic tissue was localized during operation using the isotope detector probe in six patients. The accessory spleens ranged in size from 0.5–7 cm in largest dimension. Six of the nine patients (66%) who had accessory splenectomy had complete remission of ITP and are no longer receiving steroids. No mortality was associated with accessory splenectomy but significant morbidity occurred in one patient in whom a left subdiaphragmatic hematoma developed that required surgical drainage.

Discussion

In this study, 58% of patients achieved platelet counts in excess of 150,000/μL within 1 week of operation and were weaned off steroids by the end of the third postop-

TABLE 3. *Accessory Splenectomy: Summary of Cases, Duke University 1975–1985*

	Primary Splenectomy		Accessory Spleen		
Patient #	Age/Sex	Duration of Response (Months)	Time from Initial Splenectomy (Months)	Spleen Size (cm)	Response*
1	48/F	3	9	1.8	Excellent
2	9/F	72	506	0.6	No response
3	60/F	0	40	2.5	Good
4	34/F	24	72	2.0 (×2)	Relapsed
		0	96	2.0	Excellent
5	27/F	0	1	1.5 (×2)	Excellent
6	20/F	2	156	3.0	Fair
7	25/M	72	108	1.4 (×2)	Excellent
8	47/F	0	180	1.5 (×2)	Fair
9	7/F	360	444	7.0	Good

* Excellent = platelet count >100,000/μL; no steroids. Good = platelet count >100,000/μL; steroids for limited period. Fair = platelet count >100,000/μL; receiving steroids.

erative week. This immediate response rate increased to 71% as some patients who had an initial poor response to splenectomy remitted during follow-up on steroid therapy or responded to accessory splenectomy. This pattern of response is similar to the average complete response rate of 72% reported by others (Table 4). However, patient selection among these series was not uniform. Although none of the patients received steroid therapy before 1951,[3,14–16] most patients who had splenectomy after that date had failed immunosuppressive therapy. In the current series all patients failed intensive immunosuppressive therapy except for the three patients who had urgent splenectomy.

Does presplenectomy response to steroid therapy predict platelet response to splenectomy? Mintz et al.[22] observed a postsplenectomy remission rate of 92% in patients who had responded to steroids before operation and only a 68% response rate in those who had not shown response to preoperative steroids. However, the complete remission rate reported by others among patients who showed preoperative response to steroids ranged from 67–82%[23–25] and was not different from the overall response rate of 56–85% (Table 4). In the current study none of the 75 patients who had a sustained response to immunosuppression and who could tolerate steroids needed splenectomy (Fig. 1).

Although some previous reports suggest that a long duration of medical therapy before splenectomy is associated with poor response,[22,26–28] the current data suggest that the longer duration of medical therapy among the nonresponders reflects a selection bias on the part of primary physicians who were reluctant to refer older patients for surgical therapy. Age was an important predictor of response in the current study as the nonresponders were significantly older than the responders (Fig. 4). These observations concerning the predictive value of age are similar to those previously reported by Coon[21] and DiFino et al.[24] However, age did not appear to be a significant predictor of response in the series reported by Charlesworth and Torrance[29] and by Burger et al.[30]

The selection of patients with immune thrombocytopenic purpura for splenectomy on the basis of the form of disease was recognized very early. Splenectomy was

TABLE 4. *Splenectomy for ITP, Results in 872 Collected Cases*

			Remission (%)			
Series	Year	No. of Patients	Complete	Partial	Failure (%)	Operative Mortality (%)
Spence[3]	1927	101	69 (68)	6 (6)	5 (5)	21 (21)
Wintrobe et al.[14]	1937	73	44 (60)	21 (29)		8 (11)
Evans and Perry[15]	1943	24	14 (58)	7 (29)		3 (13)
Elliott and Turner[16]	1951	68	38 (56)	11 (16)	14 (21)	5 (7)
Meyers[17]	1961	54	46 (85)	2 (4)	4 (7)	2 (4)
Jiji et al.[18]	1973	51	36 (70)	10 (20)	5 (10)	0 (0)
Schwartz et al.[19]	1980	120	106 (88)	3 (3)	6 (5)	5 (4)
Musser et al.[20]	1983	65	50 (77)	9 (14)	5 (8)	1 (2)
Coon[21]	1987	216	156 (72)	56 (26)		4 (2)
Current report	1987	100	71 (71)		29 (29)	0 (0)
Total		872	630 (72)	193 (22)		49 (6)

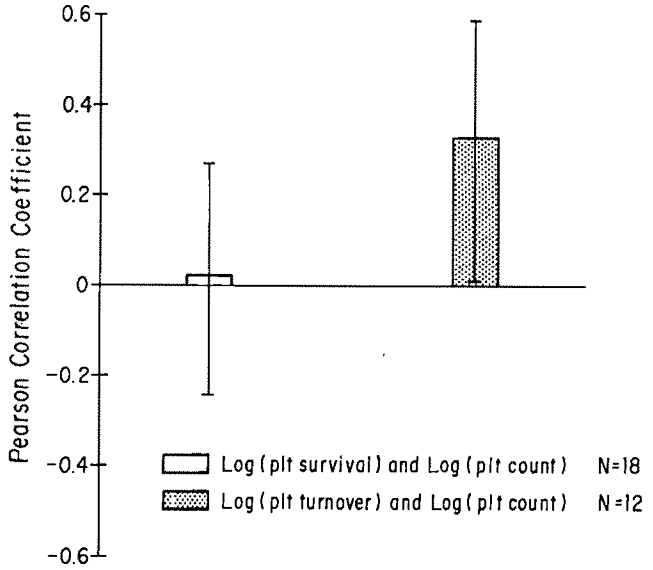

FIG. 5. Pearson correlation coefficients and relationship of preoperative indium 111 platelet survival and turnover to postoperative platelet count. No significant correlation exists between either presplenectomy log (platelet survival) and postsplenectomy log (platelet count) ($p = 0.9$) or presplenectomy (platelet turnover) and postsplenectomy log (platelet count) ($p = 0.3$).

advocated in the chronic form of ITP[2,31] and contraindicated in the acute form.[32] The acute form of the disease is seen most commonly in children and occurs 2–3 weeks after a virus infection. It often remits within 3 or 4 weeks and almost always within 6 months. Sixteen of our patients (6%) with a mean age of 9 years (range: 0.5–65 years) represented this group. The chronic form occurs most frequently in adults. The onset is insidious and is preceded by no infection or prodromes. Although some of our patients who had splenectomy were younger than 15 years of age and had had viral infections, their courses became more of the chronic type, with failure to remit after an average follow-up period of 15 months (range: 5–22 months). On the other hand, some of our adult patients had typical signs of viral illness.

The three patients who had urgent splenectomy deserve comment. Although we were reluctant to subject these difficult patients to urgent operation, their subsequently benign courses are a tribute to modern anesthetic and postoperative management. These early results encourage a continuing cautiously aggressive approach to patients in these desperate circumstances.

Platelet antibody titers failed to predict response to splenectomy as evidenced by almost similar regression lines before and after splenectomy for both responders and nonresponders (Figs. 2A and 2B). These observations confirm the earlier report of Kayser et al.[33] The strong inverse relationship between platelet count and platelet antibody titer in both responders and nonresponders, before and after splenectomy, confirmed the utility of the antibody titer as an adjunct in the diagnosis of ITP.

A correlation between the level of platelet associated IgG and the platelet count in ITP could not be confirmed by Kernoff and Malan[34] and by Kelton et al.[35]

We observed that among the responders the partial correlation coefficient between log platelet count and log antibody titer was significantly lowered by splenectomy. The coefficient among the nonresponders was unchanged by operation and was similar to that of the responders after operation (Fig. 3). An attractive hypothesis is that there is a difference in the rate of extent of clearance of platelets, initiated by the adherence of IgG-coated platelets to the surface Fc (IgG) receptors on tissue macrophages.[36] These receptors may be higher in number or may be better expressed in the spleens of responders. The number of receptors may not be as great and/or as well expressed in the spleen of nonresponders. Splenectomy would thus have little impact in this group of patients.

In newly diagnosed patients with ITP, Kernoff and Malan[34] described a significant correlation between the amount of platelet-bound antibody and the rate of platelet destruction. However, Mueller-Eckhardt et al.[37] could not correlate platelet-bound antibody with platelet survival. Although this relationship could not be examined in our patients, it is well established from our studies and others[38,39] that patients with ITP have low platelet survival. However, our study failed to confirm the value of presplenectomy platelet survival in predicting platelet response to splenectomy (Fig. 5). Moreover, platelet turnover, which reflects thrombopoiesis, ranged from subnormal to high in our patients and also failed to predict response to splenectomy (Fig. 5). Previous work by MacMillan et al.[40] has shown that cultured splenic cells in patients with ITP will synthesize IgG, which binds specifically to megakaryocytes. Other authors have also suggested that impaired thrombopoiesis plays a role in the pathogenesis of ITP.[41,42] This view might be supported by the subnormal range of turnover in some of our patients but is not true in the other patients with high turnovers. Our investigation also confirms that the pattern of presplenectomy platelet sequestration did not predict the outcome of splenectomy. This observation is in agreement with previously published chromium 51 and indium 111 studies, which show no association between the pattern of platelet destruction and platelet counts obtained after splenectomy.[39,43,44]

Although the labeling of platelets with indium 111 oxine has many advantages over the chromium 51 label for the study of platelet kinetics,[45,46] the superior gamma emitting properties of indium 111 allows more accurate

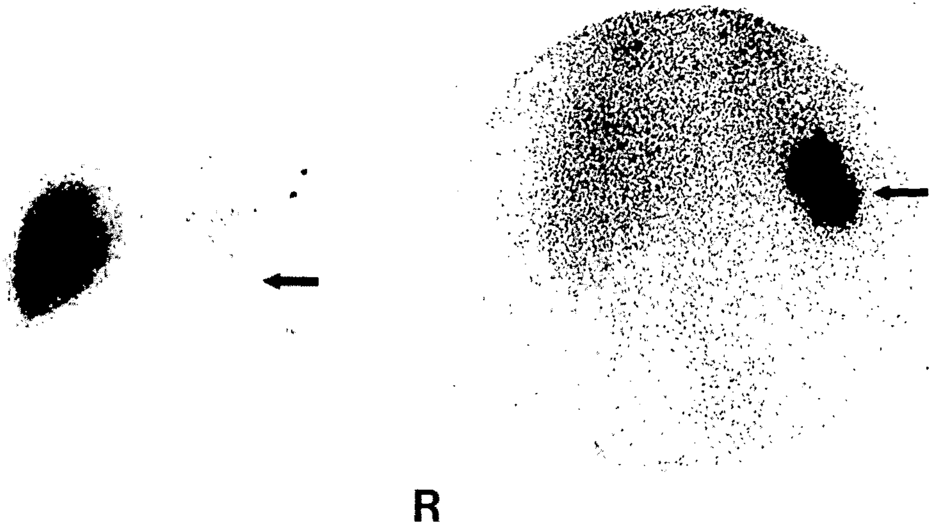

FIG. 6. Technitium 99m sulfur colloid scan (*left*) barely shows uptake in left upper quadrant accessory spleen in this previously splenectomized patient. The indium 111-labeled platelet scan (*right*) of the same patient clearly images the large accessory spleen confirmed at operation.

quantitation of absolute levels of activity within organs by quantitative scanning with the gamma camera.[47,48] This makes indium 111 an invaluable tool in the detection of accessory spleens (Fig. 6). Since the implication of an accessory spleen in the recurrence of ITP was suggested by Finkelstein[49] and the first evidence of its involvement in recurrent ITP by Morrison et al. in 1928,[50] various techniques have been used in its detection, including exploratory laparotomy,[51] thorium dioxide scans,[52] technitium sulfur colloid scans,[53] abdominal ultrasonography,[54] CT scan of the abdomen,[55] labeled RBC,[56] and indium 111-labeled platelet scan.[57] Although each modality enabled the detection of accessory spleens, there are not enough cases to compare one method with another except in one series where Tc 99m sulfur colloid was found to be inferior to CT scan and radiolabeled RBC opsonized with anti-D IgG.[58] We believe that the indium 111-labeled platelet scan offers the advantage of increased sensitivity and the possibility of studying platelet kinetics.

Re-exploration of the abdomen, especially of the left upper abdominal quadrant after initial splenectomy, may be difficult since the accessory spleen may be concealed by fat, adjacent organs, or scar tissue. Even though the location of the accessory spleen is suggested by a preoperative scan, this gives information only about the general location of the tissue. The use of a hand-held isotope detector probe during operation for this purpose was recently introduced by Wallace et al.[59] who used Tc 99-labeled RBC. We could detect accessory spleens as small as 0.5 cm using indium 111-labeled platelet scan and the intraoperative probe, and found another accessory spleen during a second operation in a patient using this method that was previously missed by a technitium 99 sulfur colloid scan.

The high incidence of accessory spleens found in the current study (18%) at the time of primary splenectomy, especially in the younger patients, should encourage a thorough search for accessory spleens and an aggressive approach looking for them in patients who do not respond to primary splenectomy. We are more enthusiastic about this approach because of the successful results in six (67%) of our nine patients and by the good results published by others in a total of 56 patients[51-66] and in whom the response was excellent in 41 patients (73%)[51,53,55,61,63-66] and moderate in the others (27%).[51,52,54,58,62,64-66]

However, an accessory spleen is not the cause of a relapse or poor response in the majority of patients. Although our nonresponders continued to be free of other diseases during their follow-up period, the association of ITP and other diseases should be kept in mind. Nonresponders should be continuously screened. Seventy-four of our patients (28%) (Fig. 1) had secondary ITP. Twenty-four had splenectomy before the primary disease was manifested. Connective tissue disorders and hematologic malignancies accounted for more than half of these cases of secondary ITP. Dameshek found that eight of 51 patients followed after primary splenectomy had definite SLE and two more had probable examples of that disorder.[67] Other reports have indicated the association of ITP with hematologic malignancies,[68-71] pregnancy,[72] hemolytic anemias,[7] and homosexuality,[73] as well as during infections.[74] The induction of thrombocytopenia by drugs such as quinidine has been said to be self-limited after discontinuation of the drug.[75] However, 10 of our patients who received diazide or quinidine progressed to chronic ITP requiring splenectomy.

Although the platelet antibody measured in the different states of secondary ITP may not be the same,[76] these observations tend to suggest that ITP is part of a more complex immune disorder. Transfusion of these patients with platelets and blood products may help in the development of isoantibodies to platelets and makes preparation for splenectomy with corticosteroids an attractive option in responsive patients. Our preliminary success with intravenously administered gamma globulin in the preparation of some of our patients for operation offers yet another option that, although currently limited by its great expense, deserves further study.

Conclusions

Although it is currently offered only to those patients in whom ITP is refractory to immunosuppressive therapy or in whom complications of steroid therapy develop, splenectomy continues to be efficacious in inducing remission of ITP in the majority of patients. Because older patients with ITP are less responsive to splenectomy, the notion that nonresponders are treated medically for longer periods before splenectomy probably reflects the selection bias of primary physicians who are reluctant to refer older patients for surgical therapy.

Although platelet antibody titer and platelet survival and turnover studies using autologous indium 111-labeled platelets were important adjuncts in the diagnosis of ITP, these tests did not predict platelet response to splenectomy in the current study. However, patients who relapse or have persistent ITP after primary splenectomy should be scanned for accessory spleens using indium 111-labeled platelets. These accessory spleens are easily localized during operation by a hand-help isotope detector probe.

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DISCUSSION

DR. A. AUFSES (New York, New York): Dr. Akwari and his colleagues are to be congratulated for presenting a beautifully documented series of 100 patients operated on for idiopathic thrombocytopenic purpura (ITP) over a 10-year period.

The manuscript that I was privileged to review is replete with extensive, prospectively derived hematologic observations and the discussion section is most complete and superbly written. I recommend its reading to all of you.

I would like to limit my remarks and questions to only one aspect of this very complete review. That is, the role of the accessory spleen in the failure of response to primary splenectomy.

Autopsy studies have shown about a 10% incidence of accessory splenic tissue. In 1969, Olsen and Beaudoin reported a large series of splenectomies performed in Ann Arbor. At operation for nonhematologic causes, the incidence of accessory splenic tissue was 4%. This incidence rose to 25% when operation was performed for either ITP or autoimmune hemolytic anemia. In that paper the authors cautiously point out that bias may have entered the picture since a more diligent search for accessory spleens was probably carried out in those patients operated on for hematologic disease.

In 1984, we reported a consecutive series of 69 patients operated on for ITP. Of 60 initial complete responders, three relapsed at 1, 2, and 5 years after operation. Nine patients were either partial or nonresponders. All 12 patients had technetium scanning and no accessory tissue was identified. We do, however, have one patient who had the primary splenectomy performed elsewhere and then relapsed after a number of years. An accessory spleen was identified by scan. This was removed by Dr. Isadore Kreel of our faculty and the patient has had a complete and sustained response.

Returning to Dr. Akwari's most interesting data, 18 accessory spleens were found at primary splenectomy in the 100 patients. Fifty-eight patients had an immediate excellent response. Of 13 patients with a poor response, five required accessory splenectomy, not recognized at the first operation, and scanning of 29 nonresponders identified seven more patients with accessory spleens of whom four were operated on. These were also not recognized at the first operation.

This gives us at least 30% of the original group of 100 patients with accessory splenic tissue, a very high percentage indeed. Might not it have been even higher?

It has been shown that it is possible in ITP to have a prolonged good response to splenectomy and still have occasional splenic tissue present. In fact, in the Duke series, four of the nine patients who had accessory splenic tissue removed at a second operation had had a response to primary splenectomy that lasted from 2 to 10 years.

My questions to the authors then are: (1) Is it not possible that some of the patients in this series as well as ours and others might still have splenic tissue remaining and be doing well? (2) Is there any explanation as to why some patients with accessory spleens will do well for prolonged periods after primary splenectomy for ITP and others do not? (3) Is it possible that some of the "accessory spleens" found at subsequent surgery were not present originally, but might represent nodules of splenic tissue developed after a fragment of spleen is spilled at the primary operation? In other words, a form of localized splenosis. Seeing the movie just now, it is hard to believe that those two lesions could have been missed at the primary operation. The first one was in the original hilum of the spleen, the second was 7 cm in diameter. Could this development of localized splenosis be the responsible agent for the late relapses? (4) Since indium-11 appears to be a more sensitive scanning isotope than technetium, should all patients who have surgery for ITP have a preoperative scan?

With a high incidence of accessory spleens, scanning might be cost effective when compared with the cost of a second operation. Certainly there is nothing more frustrating for a surgeon than to perform a splenectomy for ITP, not get the platelet response hoped for, and then worry whether an accessory spleen was left behind, or whether the patient does, in fact, have a different diagnosis?

DR. WILLIAM W. COON (Ann Arbor, Michigan): Dr. Akwari asked me yesterday to make a few brief comments concerning his manuscript. We have few differences of opinion. The immediate and sustained response rate in our recently reported series is almost identical with Dr. Akwari's. I believe one of the major points that Dr. Akwari has made, and we would certainly agree with, is that there currently is no way in a given individual to predict whether he or she will respond to splenectomy. We know some statistical bases that can help in predicting response; for example, age, as Dr. Akwari pointed out. Another observation we made is that the response rate, as you might expect, is higher in patients who respond to a burst of high-dose steroids, particularly if the platelet count goes above 100,000/mm^3. On the other hand, about half of the patients who do not get a response above 50,000/mm^3 with steroid bursts still get a response of splenectomy. Although the odds go up, there is no certainty as far as that is concerned.

We also have been unimpressed with the predictive value of platelet antibody studies. There has been no correlation in our hands between platelet antibody titers and whether the patient is going to respond to splenectomy.

One difference of opinion that we have is that we seldom believe that we need to give platelet transfusions to our ITP patients unless the platelet count at the time of operation is 20,000/mm^3 or below. In our big hematologic center we have a greater need for platelets than the supply at any given time. The ITP patient, compared with patients with other hematologic problems, has young, very hyperfunctional platelets that are circulating, and we have not encountered any bleeding problems in recent years in greatly restricting the use of platelet transfusions.

As Dr. Aufses implied, we also have been somewhat skeptical about the value of accessory splenectomy in patients who are nonresponders. Certainly there is every reason to scan a patient who responds initially to splenectomy and then relapses later. I believe there is some correlation between the size of the accessory spleen that one may encounter and the predictability of response to accessory splenectomy, and in the scan that Dr. Akwari showed, certainly with that huge splenic remnant, there would be a good chance for response, but we have performed accessory splenectomy on a number of patients without seeing any response in their recurrent thrombocytopenia.

Another observation that we have made is that, of our nonresponding patients, less than 20% are on any long-term ancillary therapy for their thrombocytopenia. Many patients will function very well with platelet counts between 50,000/mm^3 or even 30,000/mm^3 and 150,000/mm^3 without needing any subsequent treatment. The majority of those who are on any therapy are on a relatively low-dose chronic prednisone treatment.

I believe we can limit the use of cyclophosphamide or vincristine with all their potential toxic effects because even the nonresponders seldom need it.

DR. CHARLES L. WITTE (Tucson, Arizona): I congratulate the authors on their remarkable series and on an ingenious method to detect these spleens at operation. On the other hand, as some of the other discussants implied, I also interject a word of caution about the real implications of these accessory spleens. Some years ago Crosby suggested (N Engl J Med 1972; 286:1252–1254) that small remnants play little or no role in ITP, which displays great clinical variability in terms of platelet response as well as need for prolonged follow-up to ensure that these small remnants or their removal truly exert an impact on the peripheral platelet count. We are all familiar with the improved response of children over adults to splenectomy. When an IgM protein coats the peripheral platelets, as in adults, both the liver and the spleen prematurely extract platelets from the blood circulation, whereas when platelets are coated by IgG alone, as in children, splenectomy is usually highly effective.

I would like to describe three patients with ITP from my experience whose findings cast doubt on the importance of small accessory spleens in influencing the peripheral platelet count. Although I would not recommend the first approach, it nonetheless is noteworthy that one of my colleagues, a pediatric surgeon in Tucson, some years ago in a 5-year-old boy with a very low peripheral platelet count opted to do a splenectomy, which was entirely appropriate, and then placed small autoremnants into the anterior abdominal wall as an implant, presumably to protect against overwhelming sepsis. A technetium sulfur colloid scan at 2 months failed to reveal remnant tissue, and the peripheral platelet count was normal. About 2 years later, the mother returned and inquired about a palpable nodule in the boy's abdominal wall. A radionuclide heat-damaged red cell scintiscan was then obtained (slide), and on the lateral view right beneath the skin a splenic remnant is clearly visible. The child's platelet count was still 350,000/mm^3, and 4 years thereafter the platelet count remained normal despite persistence of the splenic nodule. Unfortunately over the past 1.5 years he has disappeared from follow-up.

A second patient was a 5-year-old girl (slide) in whom I tried some years ago to regulate splenic function by ligating the splenic artery close to the hilum. Subsequently I have learned that because of a rich peripancreatic and gastric collateral circulation, the effectiveness of this procedure is only temporary. Nontheless, her peripheral platelet count, which had been less than 20,000/mm^3 for over 1 year, rose promptly after operation but thereafter fluctuated widely. Four months after splenic artery ligation she demonstrated a normal splenic image on radionuclide scintiscan and her blood platelet count 12 years later is now 300,000/mm^3. She menstruates without excessive bleeding.

The final patient is a young man with Evans syndrome, which is both an autoimmune hemolytic anemia and thrombocytopenic purpura. He initially did well after splenectomy, but returned 15 years later with recurrence of thrombocytopenia, and a prominent splenic remnant was detected. This splenic fragment was removed and again he had a prompt rise in the blood platelet count. Within 6 months, however, the peripheral platelet count again dropped to 22,000/mm^3 despite lack of a residual spleen.

These patients with ITP highlight the variable nature of peripheral platelet count with and without remnant spleens and suggest that we should exert extreme caution in ascribing the clinical outcome to small residual splenic fragments after splenectomy. They also emphazise again the need for prolonged follow-up given the wide fluctuation in platelet count and even spontaneous remissions that may occur in ITP.

DR. ONYE E. AKWARI (Closing discussion): I am most grateful to the discussants. The points raised are all most interesting and reveal our ignorance in this disease.

One can say that ITP, an immune disorder, is not primarily a surgical disease, and requires close collaboration between the surgeon and the hematologist for optimum management. We continue to learn a lot from this team approach.

Dr. Aufses, I believe that splenosis is well documented in the literature, and as I remarked in my presentation, we do exercise great care not to spill any splenic tissue because of that eventuality, and the possibility of iatrogenic splenosis. I do not know, however, that there is proof that splenosis *per se* relates to recurrence of this disease. I know of no specific evidence that splenosis tissue is immunologically viable or can lead to the phenomena that are observed in this disease.

It is true that a large number of the patients have relatively large accessory spleens, but in some of these patients we found accessory spleens less than 1 cm in greatest diameter. Still when the splenic tissue was removed, the patients had a sustained response, with normal platelet counts during several years of observation. All we can conclude is that the accessory spleen must have had something to do with the disease in these patients, but the exact mechanism of its function remains to be fully elucidated.

The 30% incidence of recurrent ITP observed in this series is high. I believe it is because we search unusually meticulously for accessory spleens. I have no further explanation for that.

Dr. Coon raised many good points, and I would agree with him that currently we do not have any way of predicting response in any one patient, but therein, I believe, lies a challenge for the future.

I enjoyed seeing the transplanted splenic tissue in the abdominal wall, and was pleased to learn that the patient is doing well. I would agree with you that one would not advise doing that on a routine basis. I believe, however, that our data would suggest that the patient in question merits close observation.

Recurrence of ITP after previous accessory splenectomy occurred in one of our patients, and this was before we established our current techniques of intraoperative localization. In that patient, I believe it was patient No. 5 in our series, we identified additional accessory splenic tissue on a subsequent scan and performed repeat accessory splenectomy. The patient now enjoys a total response. One would have to conclude, cautiously, that in cases of initial failure, re-examination and repeat accessory splenectomy may be helpful in those selected cases in whom unequivocal evidence of additional splenic tissue is found.

Management of Infected Pancreatic Necrosis by Open Drainage

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Twenty-eight consecutive patients with infected pancreatic necrosis were managed by extensive unroofing of the superior retroperitoneum, blunt pancreatic sequestrectomy, laparotomy pad packing of the lesser sac over a layer of Adaptic® gauze, and scheduled re-explorations at intervals of 2–3 days (open drainage). Wounds were permitted to heal by secondary intention. All patients were maintained on intravenous hyperalimentation. Three of the 28 patients died (11%); none died of sepsis. Procedure-specific complications included: pancreatic fistula (10 patients), incisional hernia (8 patients), persistent functional gastric outlet obstruction (2 patients), retroperitoneal venous hemorrhage (2 patients), and intestinal fistula (1 patient). Limited initial experience with dynamic pancreatography and serial monitoring of acute phase reactants as indicators of pancreatic necrosis is promising. Compared with historic controls, open drainage of infected pancreatic necrosis represents a significant advance over more conventional surgical approaches. Controlled studies and more widespread experience are necessary for further evaluation of this procedure.

DESPITE SIGNIFICANT recent advances in supportive therapy and intensive care, the mortality rate from acute pancreatitis has remained constant for more than 40 years.[1-3] Today, few patients die of the well-recognized consequences of hypovolemia induced by acute pancreatitis. Rather, the development of sepsis has emerged as the principal determinant for survival in patient with acute pancreatitis surviving longer than 7 days.[2-4] In this regard, it would seem that our previous efforts to reduce mortality in acute pancreatitis have served to change the mode of death from fluid deficit to septicemia.

Pancreatic abscess is a particular case in point. In 1963, Altemeier and Alexander recommended anterior celiotomy, identification and debridement of necrosis, and closed drainage for patients with pancreatic abscess.[5] In the 25 years that this conventional surgical approach to pancreatic sepsis has been used, mortality rates have remained unacceptably high, ranging from 30–60%.[6-11] Furthermore, as many as three fourths of the deaths *after* conventional surgical debridement and drainage for pancreatic abscess have been due to sepsis.[12] These observations cast serious doubt on the efficacy of the conventional surgical approach to the management of these patients. It is becoming increasingly clear that if we are to reduce mortality in acute pancreatitis, additional approaches to the various forms of pancreatic sepsis must be sought.

Recently, infected pancreatic necrosis has become recognized as the most severe form of pancreatic sepsis, with surgical mortality rates greater than twice those of classical pancreatic abscess.[13] The current report details a 10-year personal experience using an alternative surgical procedure (open drainage) in the management of these difficult patients with infected pancreatic necrosis.

Patients and Methods

The patient population consists of 28 consecutive patients with surgically proved infected pancreatic necrosis who were seen at Grady Memorial Hospital and the Atlanta Veterans Administration Hospital during 1976–1986. Previous communications have described our earlier experiences with these patients.[14,15] Each patient had an antecedent episode of *severe* acute pancreatitis as stratified by two independent clinical classification systems (Table 1). The anticipated overall mortality rate for acute pancreatitis of this severity exceeds 50% in both systems.[9,16]

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The cause of the acute pancreatitis was believed to be alcohol in 19 patients, gallstones in three patients, Type IV hyperlipidemia in two patients, hyperparathyroidism in one patient, and three cases of acute pancreatitis were classified as idiopathic. There were 20 men and eight women with an average age of 46.1 years (range: 36–85 years).

In the initial phase of the study, the diagnosis of infected pancreatic necrosis was primarily one of suspicion; *i.e.*, progressive deterioration in a septic patient with antecedent pancreatitis. Later, computed tomography (CT) became of considerable assistance to the clinical diagnosis. Most recently, bolus contrast enhanced CT scans (dynamic pancreatography), guided needle aspiration bacteriology, and serial serum monitoring of acute phase reactants have materially assisted the clinical diagnosis of infected pancreatic necrosis. Bolus contrast enhanced CT scans were performed by the administration of iodine contrast material (400 mg/kg) by pressure injection through a large central vein catheter over 10–20 seconds. Serum levels of C-reactive protein, α-1 antitrypsin, and α-2 macroglobulin were monitored every other day in the last four patients.

Surgical exploration was begun in each patient by a left subcostal incision. Pancreatic necrosis was considered to be present when the typical grey-black necrotic material of putty-like consistency with surrounding turbid fluid was found in the lesser sac. Considerable effort was spent in determining whether the necrotic material was pancreatic or peripancreatic tissue. It was estimated at the operative table that pancreatic necrosis exceeded 30% of the gland in each of these 28 patients. Exposure of the splenic or superior mesenteric veins after debridement of the necrotic tissue greatly assisted this determination. When pancreatic necrosis was established as being present, the incision was extended and extensive unroofing of the retroperitoneum, sequestrectomy, and open packing of the lesser sac over Adaptic® gauze was carried out as previously described.[15] Pancreatic necrosis was considered infected only when smears or cultures of the necrotic material were positive for bacteria. After operation, additional debridement was carried out and dressings were changed in the operating room under light inhalation anesthesia at 2–3-day intervals. After three to five such re-explorations, dressing changes were done at the bedside. Wounds were permitted to heal by secondary intention. All patients were managed by intravenous hyperalimentation until oral feedings were resumed. Needle catheter jejunostomy for enteral feeding access has been added in recent patients.

The duration of hospitalization in these 28 patients ranged from 31 to 96 days (mean: 46 days). This time is not appreciably different from the 50–70 days required for drainage by the conventional surgical approach.[7,17,18]

TABLE 1. *Stratification of Severity in 28 Patients with Infected Pancreatic Necrosis*

Staging System	Average # Criteria (Range)	Expected Surgical Mortality Rate
Ranson and Spencer[9]	5.3 (3–8)	65%
Bank et al.[16]	1.6 (1–4)	56%

In the 10 most recent patients who had open drainage, the average length of postoperative recovery was 39 days.

Results

Twenty-five of 28 patients treated by open drainage survived (11%). A 75-year-old woman died of autopsy-proved myocardial infarction 21 days after surgery. Massive aspiration after attempts at enteral feeding for persistent gastric outlet obstruction was responsible for the death of a 65-year-old man 87 days after surgery. Sudden death in a 47-year-old man 60 days after surgery was attributed to air embolism from a disconnected hyperalimentation catheter. In none of the three deaths was persistent or recurrent sepsis a factor.

Particularly impressive was the amount of additional necrotic and infected material that was found at the scheduled re-explorations. Reaccumulation of such materials, and the discovery of additional pockets of infected necrosis at scheduled dressing changes, occurred in each patient in this series. In general, the discovery of additional necrosis became less frequent in the individual patients as granulation tissue began to appear in the base of the lesser sac. In some patients, granulation tissue began to occur as early as the third dressing change. The predominant bacteria cultured from the necrotic tissue are shown in Table 2. Anaerobic bacteria (principally bacteroides) were also cultured in seven of these patients.

Despite favorable mortality, considerable morbidity attended the hospital courses of these patients. In addition to the known pulmonary, renal, metabolic, hematologic, and regional consequences of severe acute pancreatitis, a number of complications seemingly specific

TABLE 2. *Bacteriology of Infected Pancreatic Necrosis*

Organisms	No. of Patients
Escherichia coli	12
Aerobacter	7
Klebsiella	6
Pseudomonas	2
Enterococcus	1
Total	28

TABLE 3. *Specific Complications Associated with Infected Pancreatic Necrosis and Open Drainage*

Complications	No. of Patients	Percentage
Pancreatic fistula	10	36
Incisional hernia	8	29
Gastric outlet obstruction	6	21
Temporary	4	
Persistent	2	
Retroperitoneal hemorrhage	2	7
Intestinal fistula	1	4

for open drainage occurred (Table 3). Pancreatic fistula occurred in 10 patients but could be managed by conservative means in each patient. Somewhat surprisingly, incisional hernia developed in only eight patients, despite extension of the initial left subcostal incision to a bilateral subcostal incision in 26 of 28 patients. Gastric outlet obstruction was noted in six patients, and was persistent in two patients. Unfortunately, both of the latter patients died as a direct result of attempts to find alternate methods of nutrition. Two additional patients had major retroperitoneal venous hemorrhage from the portal system (one splenic vein and one superior mesenteric vein). These episodes were controlled with great difficulty by a combination of pressure and clotting agents. Early in our experience, we attempted to accelerate wound healing by sewing synthetic mesh to the abdominal wall. In one of the two patients in whom this technique was used, a jejunal fistula developed from contact with the mesh. This approach is no longer used and wounds now are permitted to heal entirely by second intention.

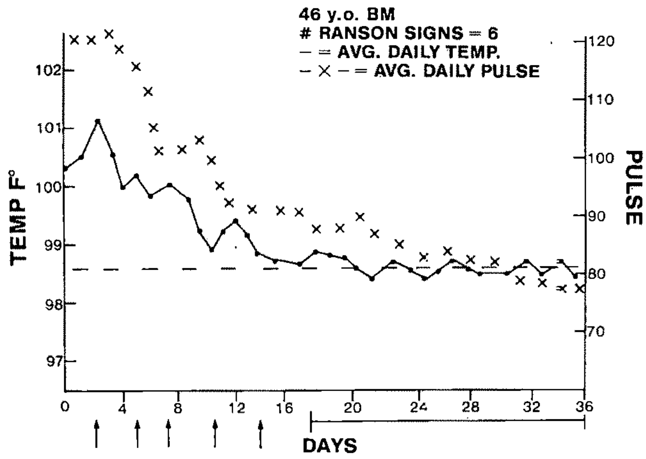

FIG. 1. Hospital course of a recent patient with infected pancreatic necrosis treated by open drainage. Arrows represent re-exploration in operating room; daily dressing changes on ward are shown by solid line.

Most importantly, none of the 28 patients subjected to open packing and scheduled re-exploration had persistent or recurrent sepsis. A representative hospital course from a recent patient is seen in Figure 1.

Dynamic CT pancreatography was correctly predictive of pancreatic necrosis in the four patients in whom it was used (Figs. 2 and 3).

Severely elevated serum levels of C-reactive protein (205 ± 30 mg/L SEM; NL < 40 mg/L) and α-1 antitrypsin (6.1 + 1.8 g/L SEM; NL 1.5–3 g/L) along with depressed valves for α-2 macroglobulin (1.5 ± 0.6 g/L SEM; NL 2.3–2.7 g/L) were found before operation in the last four patients with infected pancreatic necrosis. Values tended to normalize as the necrotic process was controlled.

Discussion

In recent years, the clinical course of patients with severe acute pancreatitis has changed. Formerly, the majority of deaths occurred early in the course of the disease, and were principally due to the consequences of hypovolemia.[1–2] More recently, however, advances in resuscitative and supportive management have all but eliminated dehydration as a mechanism of death in these patients. As a consequence of an increase in the length of patient survival, the later complications of severe acute pancreatitis (*i.e.*, necrosis and infection) are being recognized with increasing frequency. Sepsis has now become the most common cause of death in patients with acute pancreatitis who survive the first week of illness.[2–4] However, since the *overall* mortality rate in acute pancreatitis has not changed during this same period,[1–3] it seems clear that we must shift our attention to the management of sepsis if we are to make further progress in reducing mortality.

After the original morphologic classification of "hemorrhagic, suppurative, and gangrenous pancreatitis" by Fitz in 1889,[19] over 30 years passed before Moynihan recommended anterior celiotomy, debridement, and external drainage for patients with pancreatic abscess.[20] However, it was not until the landmark report of Altemeier and Alexander in 1963,[5] that these principles were widely adopted. In the 25 years that this conventional approach has been followed, operative mortality rates have remained in the range of 30–60%.[6–11] Periodic dissatisfaction with such results seemed to have been centered around the number and the types of drains used; the majority opinion being that sump suction was superior to other forms of drainage.[6,7,9,21] However, three of the largest surgical series of pancreatic abscess using the conventional approach failed to demonstrate any difference in survival regardless of the type or number of drains used.[8,10,22]

Why should the results of surgical drainage in pancreatic abscess be so greatly inferior to abscesses of other tissues? It has been claimed that 40% of patients who have conventional surgical drainage for pancreatic abscess will require re-exploration for persistent or recurrent abscesses.[23] Other workers have also noted a disturbingly high incidence of recurrent postoperative sepsis.[6,7,10,22,24,25] In an extensive review of the reported cases of pancreatic abscess in which the cause of death could be determined, we found that 76% of the postoperative deaths after conventional surgical drainage were due to sepsis.[12] These observations are sufficient to indict the conventional surgical approach. Fry and coworkers have also concluded that ineffective surgical drainage is primarily responsible for postoperative mortality in patients with intra-abdominal abscess.[26]

Why should the rate of persistent or recurrent sepsis be so high after conventional surgical drainage for pancreatic abscess? In addition to the observations that the retroperitoneum has few anatomic limitations to extensive tracking, and seems limited in its protective mechanisms against infection,[27] necrosis is a predominate feature of pancreatic abscess, and such particulate material cannot be drained by small caliber drains.[10,15,22,28] Recognition of pancreatic necrosis as a significant feature of pancreatic abscess has important clinical implications. Patients with infected pancreatic necrosis have a significantly higher mortality rate, more severe pancreatitis, increased renal insufficiency, and more profound metabolic aberrations than do patients with the more classical purulent forms of pancreatic abscess.[13] In view of these observations, a precise morphologic definition of any septic retroperitoneal process is clearly required.

Survival figures for "pancreatic abscess" may therefore be influenced either favorably (by inclusion of infected pseudocysts, suppurative peripancreatic abscess, and possibly even nonpancreatic lesser sac abscesses) or unfavorably (by including infected pancreatic necrosis). Many examples of such favorable definitions appear in the literature. In a recent review of 112 articles dealing with pancreatic abscess, we found that *only ten* authors even offered operational definitions of pancreatic abscess.[29] No two definitions were the same, and only two groups defined "pancreatic abscess" as necrosis. In view of the significantly greater mortality and morbidity of infected pancreatic necrosis, it is important that future reports distinguish between these conditions and recognize infected pancreatic necrosis as a separate clinical entity.

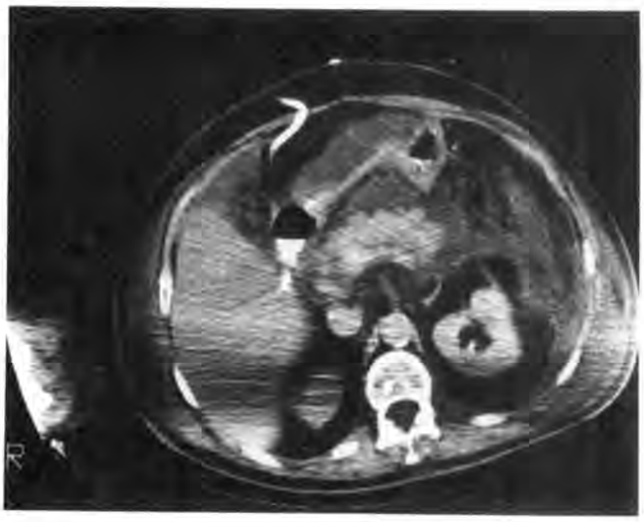

FIG. 2. Dynamic pancreatogram depicting absence of pancreatic parenchymal opacification in tail of pancreas. Necrosis of the tail of the pancreas was confirmed at surgery. Pancreatitis developed after common duct exploration (note T-tube).

The low mortality rate in the current series of patients with infected pancreatic necrosis treated by open drain-

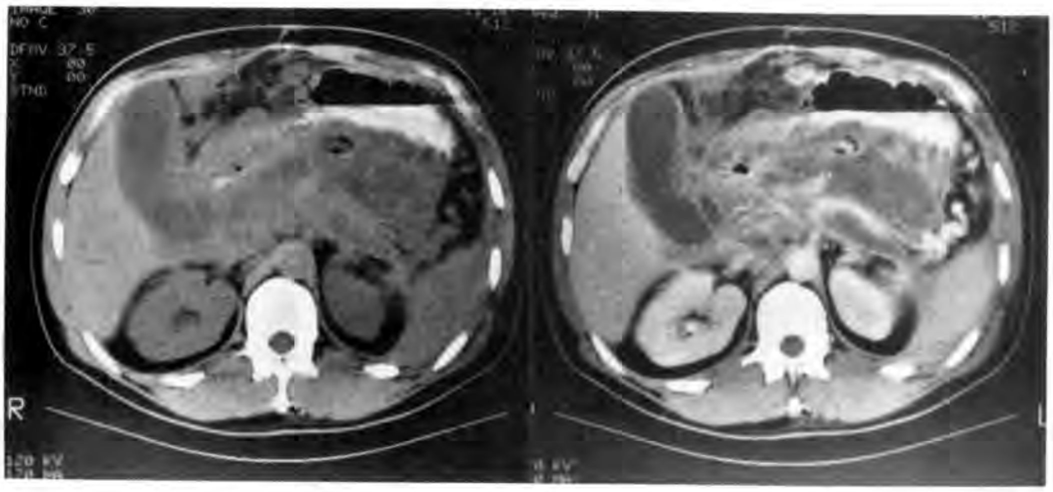

FIG. 3. Differential diagnosis of pancreatic necrosis by dynamic pancreatography. Process shown by conventional CT on left could represent either phlegmon or necrosis. After intravenous bolus of contrast material (note contrast in aorta), no pancreatic tissue could be opacified. Surgical exploration revealed extensive pancreatic necrosis.

age compares favorably with the 30–60% mortality rates from previous reports of "pancreatic abscess" using conventional drainage.[6–11] The comparison becomes even more favorable when it is appreciated that in many of the previous series pancreatic abscess was not defined as adversely as in the current report.

Dismayed by a 55% surgical mortality rate for patients with infected pancreatic necrosis treated by conventional surgical drainage in our own institution, in 1976, we devised the concept of open drainage to combat the problem of continuing necrosis and reaccumulation of purulent material after conventional drainage.[14] At that time we were unaware of previous efforts in the use of this principle. In 1928, Schmeiden and Sebening recommended that after exploration for pancreatic necrosis, "the incision should be kept wide open for many weeks because of the persistent wound and pancreatic enzyme secretion and also because of the extremely long time required for the discharge of the gland sequestra."[30] In 1968, Bolooki and co-workers reported suturing the wall of pancreatic abscesses to the abdominal skin (marsupialization) with successful results.[28] The current technique of open drainage differs from these historic precedents by extensive unroofing of the retroperitoneum, the use of nonadherent Adaptic® gauze, and scheduled re-explorations with additional debridement and dressing changes.

Favorable experiences with open drainage are also being accumulated by other workers. Pemberton and his colleagues reported a 20-year longitudinal comparison of open drainage (17 patients) with conventional closed drainage (64 patients) in which they found a significant decrease in mortality rate when open drainage was used (18% *vs.* 44%; $p < 0.05$).[31] Wertheimer and Norris salvaged 8 of 10 deteriorating patients with necrotizing pancreatitis and persistent sepsis after conventional surgical drainage by converting each case to open drainage.[32] Vogel and his associates have successfully managed 11 consecutive patients with infected pancreatic necrosis by open drainage (Vogel S, personal communication, 1987). Waclawiczek et al. reduced their surgical mortality rate in infected pancreatic necrosis from 70% using conventional surgical drainage to 17% in a group of 17 patients treated by open drainage.[33] Each of these workers have also attributed the reduction in mortality rate with open drainage to the removal of reaccumulated necrotic and infected material by the continued debridement of scheduled re-exploration and dressing changes. We continue to believe that reaccumulation of necrosis and infection accounts for the high incidence of postoperative sepsis after conventional debridement and drainage, and ultimately results in increased mortality.[14]

Warshaw and Jin have taken issue with the necessity for open drainage in patients with pancreatic sepsis, citing a 5% mortality rate for conventional closed drainage in 45 patients with "pancreatic abscess."[34] Compared with previous studies using similar conventional surgical drainage, they attribute their greatly improved survival rates to earlier diagnosis and surgical intervention, extensive debridement and drainage, and improved postoperative care. Unfortunately, they did not define "pancreatic abscess" as adversely as infected pancreatic necrosis, nor did they stratify the severity of the underlying pancreatitis. Each of these factors is known to significantly affect mortality rate.[2,13] Furthermore, Pemberton and co-workers separated their data on 81 patients with pancreatic abscess into three time periods and could not demonstrate any recent increase in survival, which if present, might have been attributable to earlier diagnosis by computed tomography or to recent improvements in intensive care.[31] These observations suggest that apples and oranges remain incomparable.

Three complications of open drainage that could be considered procedure-specific require further comment. In the Mayo Clinic series, an enteric fistula developed in 31% of patients, presumably resulting from the frequent dressing changes.[31] We have continually advocated placing a porous nonadherent petrolatum gauze (Adaptic®) next to the intestine to prevent inadvertent intestinal debridement during frequent dressing changes,[14] an important step omitted in the Rochester series. Using this approach, only one of our 28 patients had an enteric fistula. Similarly, it is recommended that Adaptic® be used to cover any major veins exposed by the process of debridement to limit the frequency of major venous hemorrhage. Less major hemorrhage is easily controlled by the packing process. Finally, functional gastric outlet obstruction has been seen in six of our 28 patients. In each of the six patients, barium studies failed to demonstrate a mechanical cause. Since prolonged delays in gastric emptying have also been noted after conventional closed drainage,[6,8] it is possible that the observed functional obstruction in our patients represents a defect in gastric or duodenal motility caused by severe pancreatitis, rather than being due to the technique of open drainage. Nevertheless, since gastric emptying did not improve in two of the six patients despite intense medical management, and ultimately led to the death of both patients, needle catheter jejunostomy for subsequent enteral feeding is now placed in an uninvolved segment of jejunum at the original exploration.

Recognition of infected pancreatic necrosis can be difficult even using currently available diagnostic modalities. Bolus contrast enhanced CT scanning (dynamic pancreatography) appears to be particularly attractive in its ability to distinguish pancreatic necrosis from the less severe edematous pancreatitis. Kivisaari and his associates described significantly decreased contrast enhancement after a rapid bolus injection of contrast material (dynamic pancreatography) in a group of nine patients who had surgery for pancreatic necrosis.[35] In a prospective study using dynamic pancreatography, Block et al. correctly predicted the presence of pancreatic necrosis in 50 of 59 patients.[36] In the four patients in the current study in whom dynamic pancreatography was used, it was of material value in both the diagnosis of pancreatic necrosis and the timing of surgery.

Favorable experiences with serum monitoring of the acute phase reactants C-reactive protein, α-1 antitrypsin, and α-2 macroglobulin to indicate the presence of pancreatic necrosis are being accumulated by several groups.[37,38] Overall detection rates have been as high as 85–90% in small groups of patients. If these serum tests maintain similar accuracy in controls and larger groups of patients with acute pancreatitis, they will represent a significant diagnostic addition. We are continuing to collect data on these tests.

In agreement with others[39–41] it has been our experience that CT-guided fine needle aspiration for smear and culture can be a valuable adjunct in determining whether a given pancreatic process is sterile or infected. This technique may prove to be particularly helpful in evaluating whether pancreatic necrosis indicated by dynamic pancreatography or serum acute phase reactants has become infected.

Open drainage of infected pancreatic necrosis appears to represent a significant advance over previous conventional techniques. Although it is likely that the final form of open drainage has not yet been described,[42] the principles of management described in this report continue to be promising and merit further study.

Acknowledgments

The author expresses his sincere appreciation to the surgical housestaff and the nurses of the intensive care units without whose dedication and attention to detail such a study would not have been possible.

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Discussion

Dr. Charles F. Frey (Sacramento, California): Dr. Bradley a number of years ago brought to our attention the open packing method of treating patients with infected necrosis of the pancreas and peripancreatic tissues. He has now accumulated a large experience and has achieved the lowest mortality reported for this otherwise lethal complication of pancreatitis. I believe Dr. Bradley's technique of dealing with infected necrosis represents a significant advance.

It is important to emphasize one semantic point that bears on this. That is, a well-loculated walled-off collection, whether it is called an abscess or an infected pseudocyst, is a different entity from infected pancreatic necrosis. Reports lumping the two together are mixing apples and oranges. Infected pancreatic necrosis occurs earlier after the onset of symptoms than an abscess. It consists of large segments of intact or infected particulate matter involving the pancreas and/or pancreatic tissues. It is usually associated with signs of gram-negative sepsis and can only be effectively managed by debridement or excision of particulate matter, and as Dr. Bradley is teaching us, by open packing and repeated debridement. The latter is made necessary by the fact that the combination of bacteria and enzymatic destruction of the pancreas and peripancreatic tissue continues after the initial debridement, creating new areas of necrosis. Abscesses, on the other hand, are easily managed by operative or percutaneous drainage as no new necrosis occurs after drainage.

I support the use of the open packing technique, which we use in our patients, as we believe it reduces the mortality and the length of hospitalization.

I would like to show two slides, and I would like comments from Dr. Bradley, which are little variations in technique.

Before we put in the open packing technique, we use a large Davol drainage catheter from one side of the abdomen to the other for irrigation purposes. (Slide) Then we place the adaptic gauze and packed over it.

The other thing I would like to ask Dr. Bradley about is that we have encountered patients in whom there has been hemorrhage at the time of the debridement with extension of infection into the spleen. We have found splenectomy should be performed under these circumstances to avoid further bleeding.

I would also like to ask the question of Dr. Bradley as to whether he has follow-up information on his patients after they have been discharged from the hospital. Dr. Braasch, a number of years ago, pointed out that many of the patients who had recovered from their pancreatic infections returned with complications of chronic pancreatitis.

Finally, I do not believe we can attribute all of the reductions in mortality to the open packing technique. The importance of other factors such as improved surgical intensive unit care, including monitoring, ventilator care, fluids and electrolytes, antibiotics and TPN, cannot be discounted and are, in my opinion, significant contributors to the reduction in mortality we are seeing in this disease.

Dr. Andrew L. Warshaw (Boston, Massachusetts): I rise in admiration of Dr. Bradley's continuing efforts to deal with these very ill patients, but I must say that I have to disagree with him on a number of points.

He and Dr. Frey have made the point that infected necrosis is different from an abscess. There is an element of difference in that some of these patients are more ill than others, but I submit that infection is not the primary difference, but whether or not there is ongoing necrotizing pancreatitis.

The infected necrosis patients do present earlier, at an average of about 10 days. The so-called pure pus collections are several weeks later, and they are often less ill but not always. At the time of operation the difference between infected necrosis and noninfected necrosis may be absolutely indistinguishable to the naked eye. It, therefore, may make little difference in terms of the treatment.

In terms of toxicity, Beger, whom Dr. Bradley quoted, has shown that the hemodynamic changes of necrotic tissue, whether or not infected, are virtually identical, and therefore, the toxic effects on the organism as a whole may be indistinguishable.

On the contrary, the patient with infected necrosis may be completely nontoxic. Percutaneous needle aspiration studies have shown in fact that a patient may have no signs of toxicity: no fever, leucocytosis or hemodynamic instability, and yet have bacteria present in the pancreatic necrosis. I remind you that Ranson's criteria are prognostic signs developed in the first 2 days of illness. They are not signs of what goes on 2 weeks later at the time of pancreatic abscess or infected necrosis.

The infection can set in as early as the fourth or fifth day, much earlier than we had previously suspected. This indicates that there may be a long indolent phase before it is clinically apparent. It would seem that the effects of infection and the ongoing enzymatic and necrotizing effects of pancreatitis combine early in some patients to generate a particularly fulminant course.

I find it difficult as well to accept the bland statement of how much of the pancreas is involved. Much of the lucent areas seen in these CAT scans is not pancreatic but peripancreatic fat. Since the tissue that is debrided is unidentifiable necrotic debris, I find it difficult to know how much of the pancreas is involved no matter how big the glob of swamp muck you pick out. In fact, as Bradley's figures show, few of these patients turn out to be diabetic in the long run. Although up to 80 or 90% has to be lost before producing diabetes, long-term studies do not show much pancreatic insufficiency after severe necrotizing pancreatitis.

The use of contrast-enhanced CT scanning is being suggested. This is a bandwagon that many are jumping on now. As far as I am aware, it has yet not been validated in any long-term study in Europe or here.

Finally, the statement that this is the best series in terms of reduction of mortality from this very difficult problem is a slight overstatement. Beger's own large study is reported as achieving about a 5% mortality rate with closed debridement and drainage. Although he does add local lavage catheters into the pancreatic bed, it is closed drainage, not packing. In our own series presented before this society 2 years ago, now up to 60 patients, the mortality over the past 7 years, and about 40 patients is also 5%. Our historical controls like Dr. Bradley's had a 40% mortality rate in the previous 5 years.

Therefore, what we are seeing in a number of different centers is a much improved survival rate resulting from a variety of different techniques: open packing, closed debridement and drainage (which is what we use), and Beger's closed debridement and drainage with addition of local lavage. Since all are accomplishing the same thing, it is probable that the common element is adequate debridement. Whatever else you do is probably less important and camouflages the basic issue.

I would like to ask Dr. Bradley at what point would he use needle aspiration techniques to determine whether or not there is infection, and would he use that information once he had it to decide whether or not to debride a patient who had extensive necrotic tissue? Do we really know the natural history of that dead gangrenous material well enough to sit back on any of them? Perhaps when the amount is small, but with large areas I am doubtful.

Dr. John M. Howard (Toledo, Ohio): I recently summarized 30 patients with massive pancreatic necrosis treated by external (closed) drainage. Debridement is the thing that I should like to emphasize as did Dr. Bradley. Repeated debridement was often required.

I would like to say that of the 30 patients, there was one death, a mortality rate of 3%. I should like to challenge my colleagues by saying that I believe in 1987, the mortality rate of acute pancreatitis should approach that of acute appendicitis. The mortality rate of pancreatic abscess should approach that of appendiceal abscess. The figures quoted in the past no longer are acceptable.

Could I show you a slide? (Slide) I would like to ask Dr. Bradley if this is a pancreatic abscess. Here is a woman 2 months into her illness. She has been receiving hyperalimentation, and is off and on antibiotics. She has been on a ventilator off and on for 2 months. The indication for operation was failure to thrive and delayed gastric emptying. Her temperature was 99–102 F over 2 months.

The lesser cavity is approached by laparotomy. A needle is inserted, and you see the pus exuding from the retroperitoneal tissue. The culture is negative. The gram stain is negative. There are many polymorphonuclear cells present.

The debridement continued with the hemostat inserted along the needle track and the massive retroperitoneal adipose tissue removed.

It is my belief that this may or may not be an abscess. The consistency and color suggests liquefying retroperitoneal adipose tissue. Perhaps we are looking at liquifaction of adipose tissue more than an exudate of infection.

I would like to show one other slide, (Slide) a patient who was operated on 11 months after the acute attack. The retroperitoneal tissue was debrided, and you see that over 11 months, this tissue had not liquefied.

It is my impression that the retroperitoneal tissue constitutes the majority of the necrotic tissue and that liquefaction in this relatively ischemic, more or less encapsulated space, proceeds very slowly.

Dr. John H. C. Ranson (New York, New York): I also would like to congratulate Dr. Bradley on the results he has achieved with this difficult problem using open drainage. Like the previous discussants, I agree that patients with infected necrosis require radical surgical debridement and that a readiness to reoperate and redebride necrotic tissue is an essential feature of their management. However, in evaluating the results reported today, it is critical to remember that major advances in diagnosis and supportive care have occurred in recent years and that the 40–60% mortality rate that Dr. Bradley ascribes to closed drainage is from an earlier era.

The report this morning prompted me to review our own experience with 29 consecutive patients managed over the past 4 years by debridement and wide, but closed section, drainage. The overall mortality rate in this group of patients was 17%, which, although not as good as that reported this morning, is much better than we had heard ascribed to this type of treatment. Among the patients who died, two deaths were cardiac without any residual sepsis, two deaths were related to hepatic failure in patients with associated cirrhosis, and one death was due to pulmonary embolism, in the only patient who died with uncontrolled sepsis. One third of the surviving patients required reoperation and redebridement, but two thirds required only one operative procedure for control of sepsis. In short, I believe that open packing may be a valuable approach for selected patients, but it is not needed for most patients.

Dr. Bradley reported in his abstract that his patients had more than 30% glandular necrosis, and like Dr. Warshaw, I would like to ask him how this was quantified. Certainly, contrast-enhanced computed tomography may not reliably differentiate, I believe, fluid from necrotic tissue, and certainly was not available, as Dr. Bradley said, for the whole period of his study. Measurement of weight of debrided tissue may be a valuable index of the extent of necrosis but cannot, I believe, reliably differentiate pancreatic from peripancreatic tissue necrosis.

If we did use this last criterion, our one death with uncontrolled sepsis would have been classified as having 100% necrosis, and, in this particular patient, this was combined with duodenal and colonic necrosis, which brings up my last question for Dr. Bradley.

Three, or about 10%, of our recent group of patients, have had necrosis of a portion of the duodenum in addition to their other infected necrosis. I would like to ask him if he has observed this problem, and if so, how does he approach it in his patients managed by open packing?

Dr. J. Pemberton (Rochester, Minnesota): Thank you for allowing me to read the manuscript and for extending an invitation to discuss this fine paper.

You are to be congratulated for achieving such an enviable mortality rate for one of the most devastating complications facing patients with pancreatitis.

I would like to lend support from our institution to you and to others who are attempting to define precisely the pathologic process of pancreatic abscess. Your term "infected pancreatic necrosis" is a good one, aptly descriptive and accurate. Such a term qualitatively describes a group of patients with pancreatic abscess who have the most aggressive form of this lethal complication.

Further understanding of this particularly difficult problem will be helpful in classifying such patients in the future. Moreover, you have nicely documented the severity of the predisposing episode of pancreatitis. The severity scores in your patients were high and consistent with an expected mortality of greater than 50%.

That the surgical procedure used achieved the desired goal is illustrated by the fact that no patient in your series had sepsis after operation. At Mayo, the persistent sepsis rate after operation was 47%, even after open drainage. We defined sepsis, however, based on both laboratory and clinical parameters, and I wonder if your definition and ours were the same? Nevertheless, we need to do better.

Your technique for open drainage deserves comment. As you might remember, in commenting on our report in 1985, you suggested protecting the base of the lesser sac and the abdominal viscera with Adaptic® gauze and/or Silastic® sheeting to decrease fistula and rebleeding rates. Indeed, the incidence of enteric fistula reported today is commendably low. I and others at our institution have heeded your advice, and in addition, in some cases have used a heavy plastic zipper, described by Stone, to prevent drying of those packs and subsequent debridement of the viscera.

Your report stimulated us to update the Mayo series of 81 consecutive patients with this problem. Eight additional patients were identified between 1985 and 1986. Of the five patients treated by controlled open drainage, one patient, or 20%, died. Of the three patients treated by closed drainage, all died. These most recent results, therefore, continue to support the use of open drainage in most patients with severe pancreatic abscess and necrosis.

I have two brief additional questions. Do you ever use a zipper?

Your 28 patients had 28 organisms cultured. Apparently no patient, therefore, had a polymicrobial infection. Typically, between 10 and 66% of such patients will have multiple organisms cultured from the retroperitoneum. Such polymicrobial infections may be more difficult to treat than monomicrobial infections. Although your patients had severe pancreatitis and therefore were at high risk of death, were they less difficult to manage because most of their infections were monomicrobial?

Dr. David A. Dreiling (New York, New York): I have three brief questions: (1) How long was the follow-up? (2) How many of the patients treated stopped drinking because this leads to the third question? (3) Have you observed any patients who were diabetic who lost their diabetes, and have you observed any patients who showed a malabsorption who lost that dysfunction? Many of these patients do regenerate, and I have had a patient whose total pancreas was necrotic and I could see the duodenal curve, etc., and within 18 months, his pancreatic function returned to normal. I am very interested in the possibility of pancreatic regeneration even in these severely ill patients.

Dr. George H. A. Clowes, Jr. (Boston, Massachusetts): I want to make a brief report on a carefully studied series of pancreatic necroses in which we looked at the protein metabolism in 10 patients. Two of these patients, who were cirrhotic, died. On the other hand, we had a number of patients who had liver failure associated with the presence of pancreatic septic process. You have heard me talk about the "central plasma clearance rate" of amino acids. I simply want to report that those who survived had an average value of 195 mL/m^2/min, and that those who died were in the range of 100 mL/m^2/min, which is significantly lower.

The importance of this is that Dr. Bradley is applying a real surgical principle of removing the stimulus that causes the trouble throughout the rest of the body, and I would just ask him to tell us whether with his procedure, he did not see a fairly rapid improvement in other systems. Did the patients get off the ventilator promptly? Did their liver function improve by whatever method of assessment you used?

DR. EDWARD L. BRADLEY, III (Closing discussion): I am most grateful to the discussants not only for their perceptive but also stimulating questions. I wish, indeed, I had all the answers for you this morning. Surgery in acute pancreatitis is still in its infancy. I believe over the next 10–15 years we will improve our indications and procedures. Having said that, let me address the specific questions.

Dr. Frey, thank you very much for your kind words. We do not use catheters as part of our open drainage technique. We had significant trouble when we were using the large-bore closed drainage catheters with erosion into blood vessels and into various pieces of intestine.

Dr. Frey also asked about whether we have seen hemorrhage; yes, we have. We have seen if from the splenic vein and from the superior mesenteric vein, and it certainly got our attention on both occasions. However, it does respond well to packing, part and parcel of our technique. However, we do recommend that you place Adaptic® gauze over any exposed vessels.

Dr. Frey asked for follow-up information. We have an average 5-year follow-up for this group. Within that period we did not see any of the typical changes of chronic pancreatitis.

Dr. Howard, you are to be congratulated for your low mortality rate with closed drainage in patients with pancreatic abscess. With regard to the slide you showed us, we could consider that to be liquified fat necrosis, possibly in a patient who had peripancreatic necrosis.

Dr. Ranson also has experienced low morbidity and mortality from his patients with closed drainage, and has suggested that recent changes in intensive care may have accounted for a significant portion of that result. I have no doubt that we are much smarter than we used to be in this regard, and certainly I believe patients are being better taken care of in our institution than they were 5–10 years ago. However, if you look at this particular question from a more critical viewpoint, such as the people from Mayo Clinic did when they reported their experience with open drainage in 1984, you may reach a different conclusion. They divided their data into three periods. The most recent period included all of the recent modalities such as CT scans, ICU support, and needle aspirations, and they did not find any change in mortality that they could attribute to earlier diagnosis or improved survival through better care in the intensive care unit. Accordingly, the question of why we are achieving these low mortality rates with this technique is open for further study. It is our belief that we are achieving these results because of the repetitive removal of persistent or recurrent infected necrosis.

Dr. Ranson has questioned whether we need to do open drainage if we are prepared to reoperate. In the abstract, the answer is no. However, as I told you, three quarters of the deaths in *postoperative* patients with infected pancreatic necrosis have been from sepsis. Clearly, that means that there has been reluctance to re-explore these patients in the past. Today, if one wishes to debride and close a patient with infected necrosis, one must observe these patients much closer than they have been observed in the past, and be willing to reoperate at a relatively frequent level.

Dr. Pemberton, thank you for updating the Mayo Clinic series. I am pleased that you are continuing your good results. We have not used the zipper and have not found it necessary.

The particular bacterial floral was predominantly monomicrobial, although we did have anaerobic bacteria in some of the patients along with the aerobic bacteria.

Dr. Dreiling, our follow-up, as mentioned, is 5 years. We have seen malabsorption in these patients, which probably reflects the degree of pancreatic necrosis.

Several of the questioners asked how we could tell whether the necrosis was pancreatic or peripancreatic. It is not always easy. In situations where one can visualize the splenic vein or the superior mesenteric vein, after you have done the debridement, I believe you can be reasonably certain that the pancreas is missing. Furthermore, we have had the opportunity to do ERCP on nine of these patients after operation, and in eight of the nine, at least half of the pancreatic duct was not visualized. I believe we can be sure in the that group of patients that we certainly have pancreatic necrosis.

Dr. Warshaw, has asked a series of stimulating questions. He specifically asked about necrosis *versus* infected necrosis, and, whether in fact, they are different. The only data that I know that bear on this question are the data from Dr. Beger's study. Mortality rate for noninfected necrosis was 8%, and was 32% for infected necrosis. This is a significant clinical difference.

He asked us about our classification system and reminded us that Dr. Ranson's classification is one that is done in the first 48 hours. We also classified these patients with Banks' criteria, which, of course, are continuing criteria. In both classification systems, the mortality rate should have exceeded 50%.

We agree that dynamic pancreatography is not yet validated, and we are currently conducting a prospective study to investigate whether it is going to be useful in the management of the timing of operation in these patients.

We use needle aspiration only when we see an avascular area on our dynamic pancreatogram. We do not advocate doing needle aspirations in every patient with acute pancreatitis, but only if the patient shows evidence of what we consider to be focal necrosis and clinical sepsis.

Your results in patients with pancreatic abscess, like those of Dr. Ranson's and Dr. Howard's, are to be commended because they are equally low. However, patients with infected pancreatic necrosis have a higher mortality rate and a greater incidence of multiorgan failure than do patients with pancreatic abscess. In our opinion, infected necrosis requires open drainage.

(Slide) This, ladies and gentlemen, is an apple. (Slide) And that is an orange.

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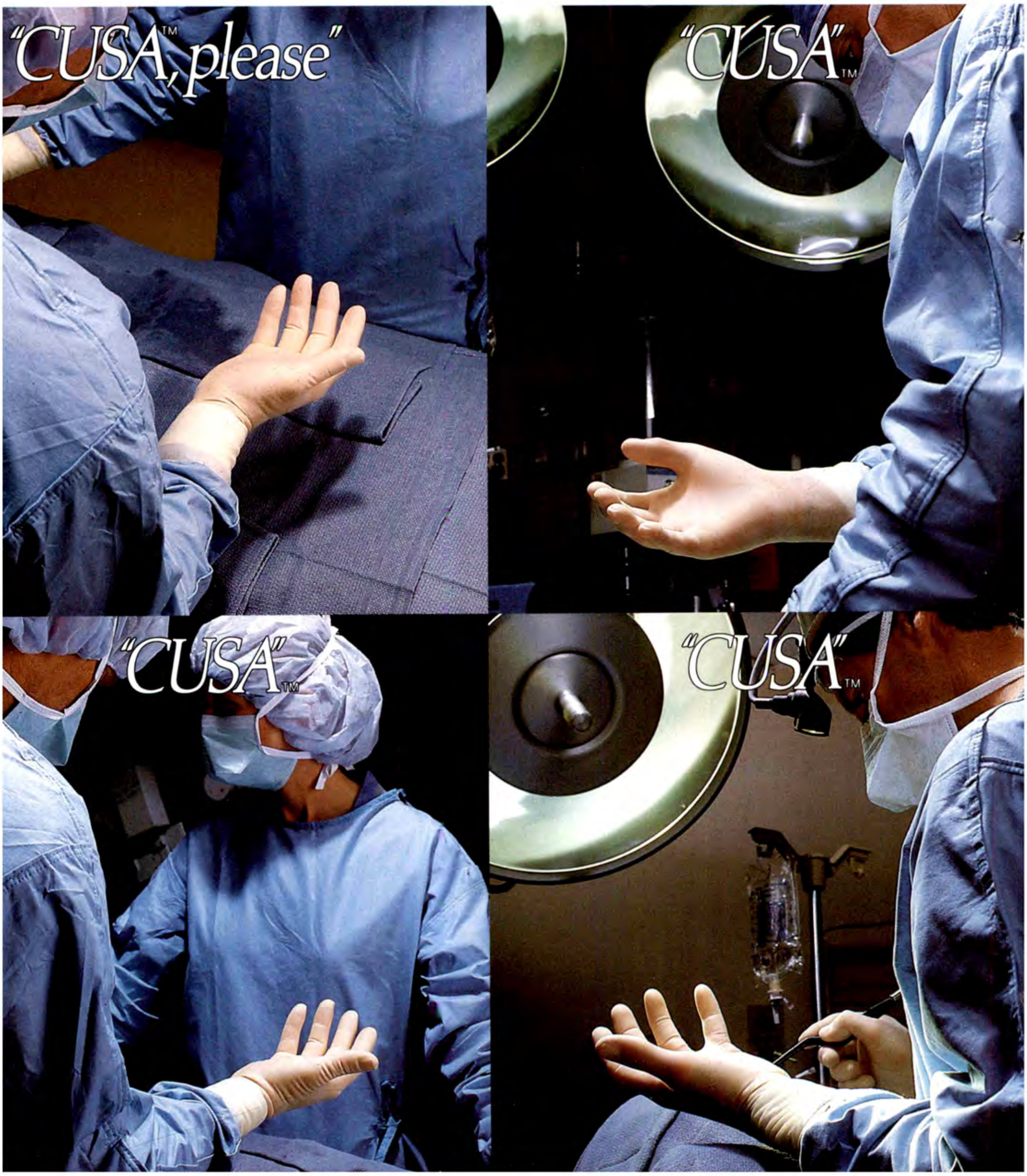

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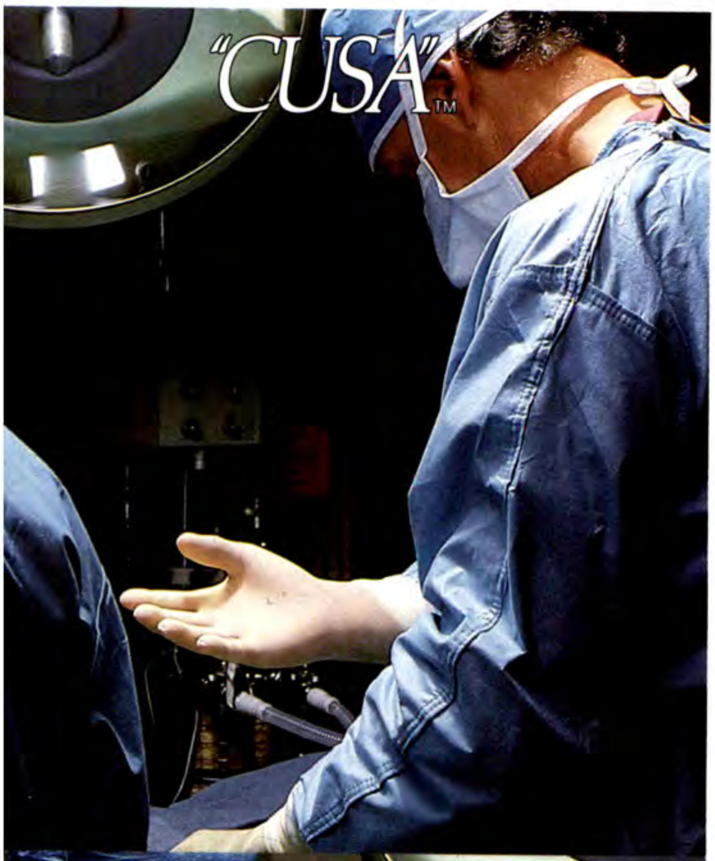

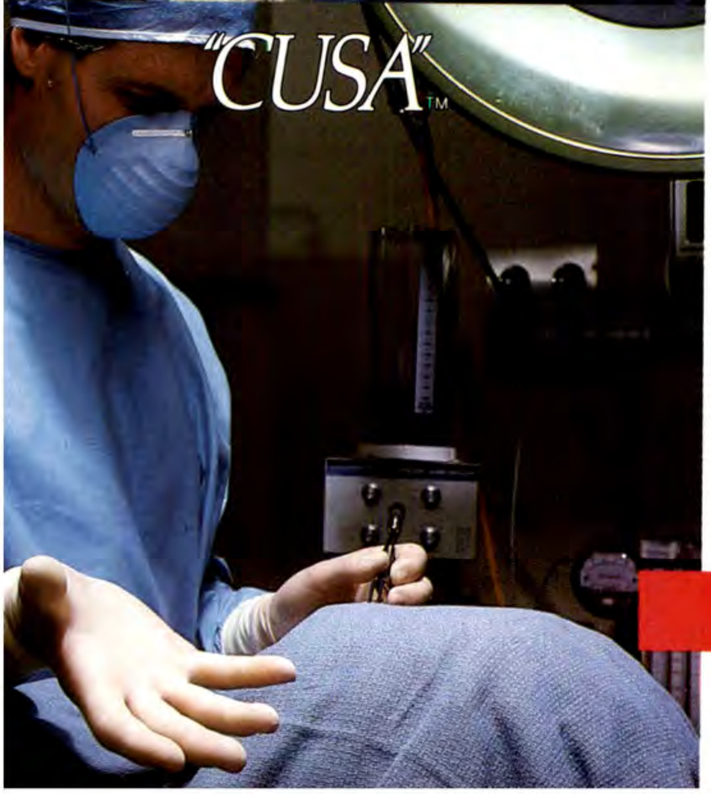

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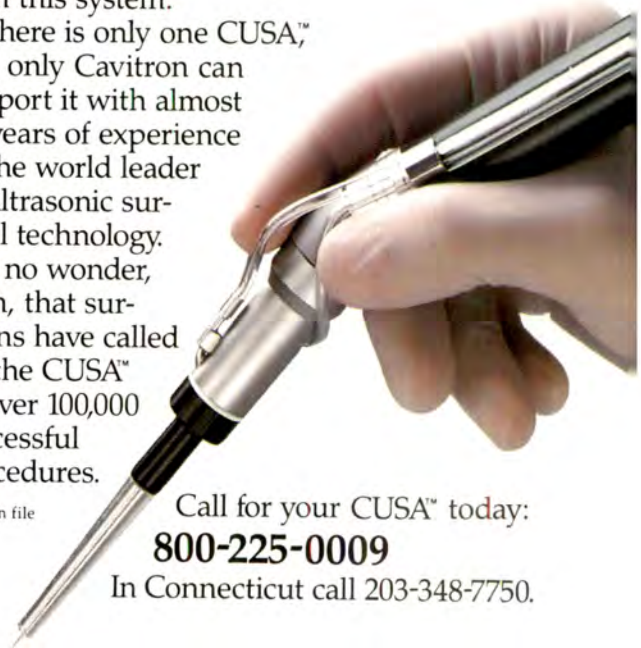

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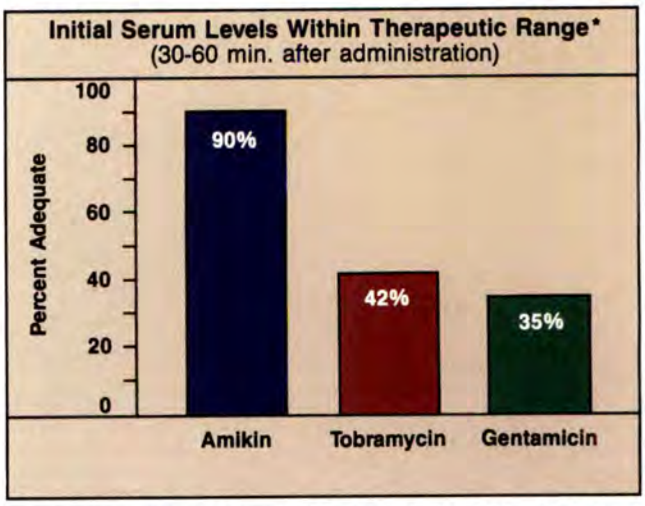

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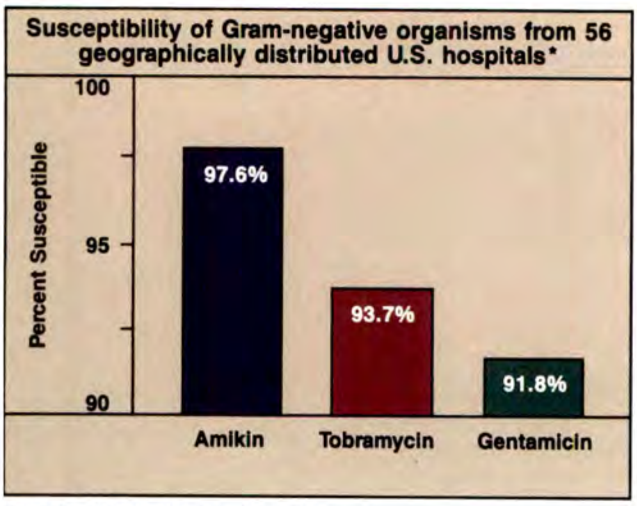

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Patients treated with aminoglycosides should be under close clinical observation because of the potential ototoxicity and nephrotoxicity associated with their use.

Ototoxicity, both auditory and vestibular, can occur in patients treated at higher doses or for periods longer than those recommended. The risk of amikacin-induced ototoxicity is greater in patients with renal damage. High frequency deafness usually occurs first and can be detected only by audiometric testing. Vertigo may occur and may be evidence of vestibular injury.

The ototoxicity potential of amikacin in infants is not known. Until more safety reports become available, amikacin should be used in infants only in those specific circumstances when susceptibility testing indicates that other aminoglycosides cannot be used or are otherwise contraindicated, and when the infant can be observed closely for evidence of toxicity.

Aminoglycosides are potentially nephrotoxic. Renal and eighth-nerve function should be closely monitored in patients with known or suspected renal impairment and also in those whose renal function is initially normal but who develop signs of renal dysfunction during therapy. Such impairment may be characterized by decreased creatinine clearance, the presence of cells or casts, oliguria, proteinuria, decreased urine specific gravity or evidence of increasing nitrogen retention (increasing BUN or creatinine).

Evidence of impairment in renal, vestibular or auditory function requires discontinuation of the drug or dosage adjustment.

Serum concentrations should be monitored when feasible, and prolonged peak concentrations above 35 mcg/ml should be avoided. Urine should be examined for increased excretion of protein, the presence of cells and casts, and decreased specific gravity.

Concurrent and/or sequential use of topically or systemically neurotoxic or nephrotoxic antibiotics, particularly kanamycin, gentamicin, tobramycin, neomycin, streptomycin, cephaloridine, paromomycin, viomycin, polymyxin B, colistin and vancomycin should be avoided.

AMIKIN should not be given concurrently with potent diuretics (ethacrynic acid, furosemide, meralluride sodium, sodium mercaptomerin or mannitol). Some diuretics themselves cause ototoxicity, and intravenously administered diuretics enhance aminoglycoside toxicity by altering antibiotic concentrations in serum and tissue.

CONTRAINDICATIONS

A history of hypersensitivity to amikacin is a contraindication for its use.

WARNINGS

See "Warning" box above.

PRECAUTIONS

AMIKIN is potentially nephrotoxic, ototoxic, and neurotoxic. The concurrent or serial use of other ototoxic or nephrotoxic agents should be avoided either systemically or topically because of the potential for additive effects. Such agents include antibacterial drugs such as kanamycin, gentamicin, tobramycin, neomycin, streptomycin, cephaloridine, paromomycin, viomycin, polymyxin B, colistin and vancomycin as well as certain diuretic agents such as ethacrynic acid or furosemide.

Ototoxicity — See "Warning" box.

Nephrotoxicity — Since AMIKIN is present in high concentrations in the renal excretory system, patients should be well hydrated to minimize chemical irritation of the renal tubules. Kidney function should be assessed by the usual methods prior to starting therapy and daily during the course of treatment.

If signs of renal irritation appear (casts, white or red cells or albumin), hydration should be increased. A reduction in dosage (see "Dosage and Administration") may be desirable if other evidence of renal dysfunction occurs such as decreased creatinine clearance, decreased urine specific gravity, increased BUN, creatinine or oliguria. If azotemia increases or if a progressive decrease in urinary output occurs, treatment should be stopped.

Note: When patients are well hydrated and kidney function is normal the risk of nephrotoxic reactions with amikacin is low if the dosage recommendations (see "Dosage and Administration") are not exceeded.

Neurotoxicity — Neuromuscular blockade and muscular paralysis have been demonstrated in the cat with high doses of amikacin (188 mg/Kg). The possibility of neuromuscular blockade and respiratory paralysis should be considered when amikacin is administered concomitantly with anesthetic or neuromuscular blocking drugs. If blockade occurs, calcium salts may reverse this phenomenon.

Other — Cross-allergenicity among aminoglycosides has been demonstrated. As with other antibiotics the use of amikacin may result in overgrowth of nonsusceptible organisms. If this occurs, appropriate therapy should be instituted.

Pregnancy — Reproduction studies have been performed in rats and mice and have revealed no evidence of impaired fertility or harm to the fetus due to amikacin. There are no well-controlled studies in pregnant women but investigational experience does not include any positive evidence of adverse effects on the fetus. Although there is no clearly defined risk, such experience cannot exclude the possibility of infrequent or subtle damage to the fetus. AMIKIN should be used in pregnant women only when clearly needed.

It is not known whether this drug is excreted in human milk. As a general rule, nursing should not be undertaken while a patient is on a drug since many drugs are excreted in human milk.

ADVERSE REACTIONS

Ototoxicity — See "Warning" box.

Nephrotoxicity — Albuminuria, presence of red and white cells, casts, azotemia and oliguria have been reported.

Other — In addition to those described above, other adverse reactions which have been reported on rare occasions are skin rash, drug fever, headache, paresthesia, tremor, nausea and vomiting, eosinophilia, arthralgia, anemia, hypotension.

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Durham, North Carolina

The Impact of Illness on World Leaders. Bert Edward Park. 377 pp. Philadelphia: University of Pennsylvania Press. 1986. $24.95.

PATHOGRAPHY, the role of illness in a person's life story, has long been a theme of interest. Major illness, of course, may play any number of roles in the lives of the sufferers, but it becomes especially fascinating when a serious study of its effects on artistic creativity or on leadership abilities is done. In this continuously engaging book, Dr. Bert Park, a practicing neuro-surgeon, guides us through the devastating effects of the aging process and neurologic disorders in the leaders of the western world during much of the twentieth century.

Beginning with the American president during the years of World War I, Dr. Park, in an extensive review of the case of Woodrow Wilson, concludes that he suffered from lacunar infarcts from a series of small strokes brought on by severe and prolonged hypertension. Some of the most critical decisions of the Paris Peace Conference were made by an impaired leader, and his battle for American participation on the League of Nations is retold here in light of Wilson's increasing inabilities. The extreme effects of the aging process on Paul von Hindenburg, the German leader who handed the reins of government to Adolf Hitler, the British prime minister Ramsey MacDonald, and the Polish leader Josef Pilsudski are examined in light of future events. Alzheimer's disease in MacDonald's case played a role in his relationship to both England's friends and potential foes.

The literature about Adolf Hitler is sizeable, but much of the pathography has turned on psychiatric questions. In a well-argued chapter, Park makes an excellent case for an organic brain disease, especially temporal lobe epilepsy and Parkinsonism, accompanied by chronic cholecystitis and flagrant over-medication or the syndrome of polypharmacy. This and the Wilson chapters are the longest, yet they are so well written that any reader, especially one with medical knowledge, will be pulled from page to page by the great drama.

Franklin D. Roosevelt's chronic obstructive pulmonary disease, congestive heart failure, and severe hypertension all took their toll, especially by the end of the third term. Park argues that despite his increasing incapacities, Roosevelt gave up little at Yalta. Finally, the British leadership was seriously compromised by strokes suffered by the aging Winston Churchill and amphetamine addiction of Anthony Eden.

Space does not allow fuller discussion of the many implications of this superb book. But surely the role of the presidential physicians and the public's need and right to know the facts have changed, but the question the author raises is whether we have learned enough from past experiences of compromised leadership?

GERT H. BRIEGER, M.D.
Baltimore, Maryland

Current Therapy in Vascular Surgery. Calvin B. Ernst, James C. Stanley. 469 pp. Philadelphia: B. C. Decker Inc. 1987 $68.50.

THIS BOOK consists of a series of short presentations by a large number of experts. The major thrust is a focused discussion of most of the many topics of interest in vascular surgery presented as contemporary thought on the topics by an individual author rather than being an exhaustive review of the subject. The editors have asked the authors to reflect his or her own personal views and experiences and no references to the literature are cited.

The editors have been very successful in their effort to evaluate *current* therapy. In the preface they say they wanted to provide a book that is not out of date before it is read. This book is very much up to date. They wanted to provide a book of use to medical students and residents, as well as experts in the field, and they have achieved that too. They also have picked topics that span the simple type problems such as ulcers in the diabetic foot or varicose veins, to the esoteric such as carotid body tumors or celiac artery entrapment. Controversy is not avoided, *e.g.*, nonresectional therapy of aneurysm or surgery for carotid artery kinks. Nonsurgical approaches are aired such as that for carotid artery stenosis and thrombolytic therapy.

The text is thorough, topical, well written, and readable. The first section I read (retroperitoneal approach to the aorta) was as interesting as was the last, thoracofemoral bypass. I enjoyed the whole book very much and will refer to it myself, I am sure, often. I would highly recommend it as being similarily enjoyable and useful to others.

WILLIAM M. ABBOTT, M.D.
Boston, Massachusetts

Rob & Smith's Operative Surgery: Thoracic Surgery, 4th Edition. Hugh Dudley, David Carter (General Editors), John W. Jackson, D. K. C. Cooper (Consultant Editors). 380 pp. St. Louis: Mosby/Butterworths. 1986. $99.95.

IN THIS FOURTH EDITION of *Rob & Smith's Operative Surgery*, the editors have acknowledged the trend toward specialization into either cardiac or thoracic surgery by publishing the volume on general thoracic surgery separately, in contrast to previous editions. Thirty-seven authors have contributed 42 chapters covering virtually the entire list of thoracic operations: chest wall, mediastinal, pulmonary, and esophageal (*oesophageal* in this text). Though the authors are predominantly British, there are several from Canada, the United States, South Africa, Yugoslavia, and Germany, thus providing an international flavor.

In each topic, the operative procedure is presented in step-by-step fashion with numerous illustrations. Primary emphasis is on the technical procedure and is given in detail; the preoperative and postoperative management, complications, and results are generally discussed in summary form.

The numerous authors and artists provide variability to the style of the presentations. They also evidence the wide range of choice among surgeons individually and geographically for the type of incision, suture material, use of the stapler, prosthetic material for chest wall reconstruction, anesthesia, etc. Thus, the reader is provided excellent descriptions of operative techniques, and simultaneously notes the option of individual choice about some parts of the procedure.

Descriptions of the various muscle and omental flap procedures used for chest wall, pleural, and sternal operations and mention of newer anesthetic techniques (unilateral intubation, high frequency ventilation, and epidural analgesia) would enhance the volume and make it more complete. Also noted is the omission of operations for Zenker's diverticulum. However, these are insignificant detractions from the book's overall value.

The book is a compendium/atlas of thoracic operations and provides an easily understandable and comprehensive review of "general thoracic" surgical operations. It will be of great benefit to general and thoracic surgeons alike.

C. FREDERICK KITTLE, M.D.
Chicago, Illinois

Oxygen Transport in the Critically Ill. James V. Snyder, Michael R. Pinsky. 554 pp. Chicago: Year Book Medical Publishers. 1987. $74.95.

THE PROMISE OF THE TITLE is well fulfilled in this excellent textbook. As critical care practice has become divided into organ-specific interests, the idea of a unifying focus for patient management has been forgotten. This text reinforces the importance of the maintenance of oxygen metabolism as the core of organ system preservation in critical illness. A major difference between this and other similar works is the attention placed on basic principles within the framework of clinical care. The authors divide the book into six basic areas that deal with the areas of oxygen supply and demand, regulation of oxygen transport, cellular oxygenation, clinical evaluation of oxygen transport, ventilatory support, and circulatory support, respectively. Where appropriate, as in the section on mechanical ventilatory support, the authors discuss the physiologic basis for support techniques and continue to describe their clinical application. This logical approach works well and is stimulating for the reader. Indeed, the text may well serve as a basis for further reading in many areas because the reference sections in each chapter are well researched and up to date.

In the preface, the authors hope to "present the physiologic and therapeutic paradigms that incorporate recent insights and prepare the reader for the anticipated increasing focus on regional pathophysiology and treatment." To accomplish this goal, the editors have assembled 37 contributing authors, each of whom follows the theme and begins by detailing the physiology that underlies his/her contribution. At no point is the clinical contribution to patient management forgotten, but the importance of laboratory assessment as an indispensable adjunct to sophisticated management techniques is highlighted. It is interesting to note that increased interest is being placed on oxygen metabolism, especially with the clinical use of multiple sophisticated monitoring devices. In fact, the technology is reinforcing the importance of basic physiology in the management of critical illness. The Society of Critical Care Medicine has published a textbook devoted to the subject of oxygen metabolism, and the subject is both timely and fundamental to patient care.

In summary, this textbook should enjoy wide popularity. It is well written, informative, and up to date. This is not a simple restatement of the shunt equation or another discussion of mechanical ventilation or the Starling curve revisited. Rather, it is an attempt to integrate the practical aspects of oxygen transport with the physiologic requirements of the organism. In this regard it is highly successful, and it will remind each reader of the intellectual inadequacies of daily practice. Perhaps its greatest success will be in the stimulation of the critical care practitioner to initiate new discussions on forgotten subjects and to investigate the vagaries of tissue metabolism. It is unlikely that any reader will remain immune to this challenge.

PHILIP D. LUMB, M.B., B.S.
Durham, North Carolina

Trauma: Clinical Care and Pathophysiology. J. David Richardson, Hiram C. Polk, Jr., Lewis M. Flint. 597 pp. Chicago: Year Book Medical Publishers. 1987. $65.00.

IN THE PREFACE, the editors state that this book is intended "to describe in detail methods of treating various injuries encountered in clinical practice" and "to provide insights into the basic pathophysiology that is operative in a variety of injured states." To accomplish this they have assembled a group of 40 contributors, 27 of whom are from the University of Louisville.

After introductory chapters on epidemiology and organization of trauma care, there are seven chapters dealing with the pathophysiology of problems common to the trauma patient, including shock, infection, organ failure, hemostasis, catabolism, and wound healing. Each chapter is concise and well written, and most chapters have extensive and current references. Especially well done are the chapters on host defense and organ failure (222 references), burn pathophysiology, respiratory pathophysiology, and wound repair (215 references).

The subsequent 11 chapters deal with the clinical evaluation and management of specific injuries, including facial trauma, thoracic and abdominal injuries, neck trauma, and pediatric trauma. Subjects are treated regionally rather than systemically, *i.e.*, the chapter on neck trauma covers vascular and aerodigestive injuries in the cervical region, whereas the chapter on thoracic trauma covers similar subjects in the chest. For the most part, these chapters are authored by the Louisville faculty drawing on their vast clinical experience. The editors emphasize this in the preface, pointing out the extensive contributions Louisville surgeons have made to trauma care for the past 75 years. Although the Louisville experience is evident, the recommendations regarding diagnosis and treatment are not parochial. The chapters on abdominal trauma and thoracic injuries are especially comprehensive with 131 and 94 references, respectively. The chapter on urologic trauma contains a section on injuries to the external genitalia, a subject treated poorly or not at all in previous texts. The final chapter on ethical, moral, and legal issues in trauma care contains useful information for the surgeon practicing in today's litigious society.

This book is written in clear and practical terms. Major points are printed in boldface type for emphasis and quick review. The text is well illustrated and the algorithms in the chapters on pathophysiology are easy to understand. The only deficiencies are minor. There is no overview chapter on initial management, evaluation, and injury priority. The chapter on epidemiology is too superficial and the chapter on trauma systems lacks information on triage, trauma registries, cost, and outcome analysis.

This is a substantial contribution to the trauma literature because it amalgamates the pathophysiology of injury with sound recommendations for clinical management. It has broad appeal and is recommended for the surgical resident and the practicing surgeon alike. Clearly, the editors have accomplished their purpose.

STEVEN R. SHACKFORD, M.D.
San Diego, California

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David C. Sabiston, Jr., M.D.
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Department of Surgery
Duke University Medical Center
Durham, North Carolina 27710

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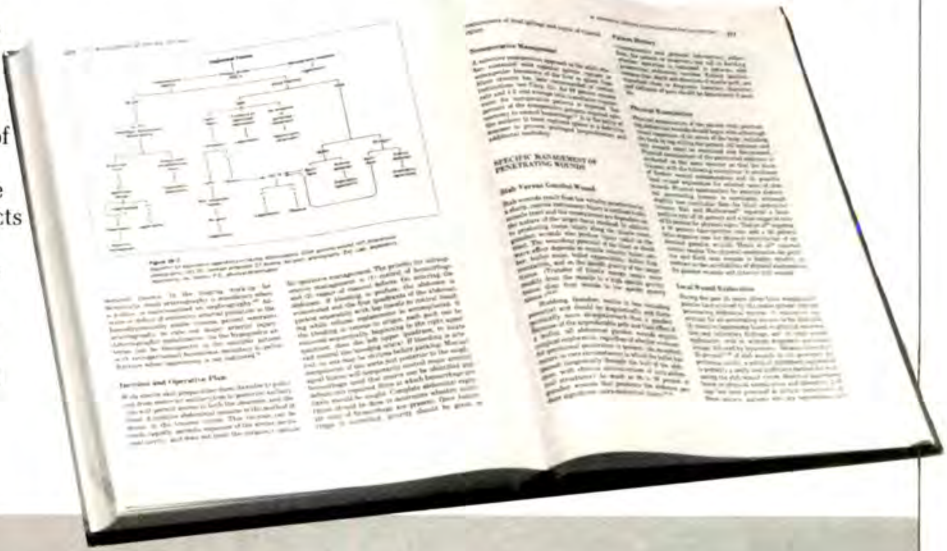

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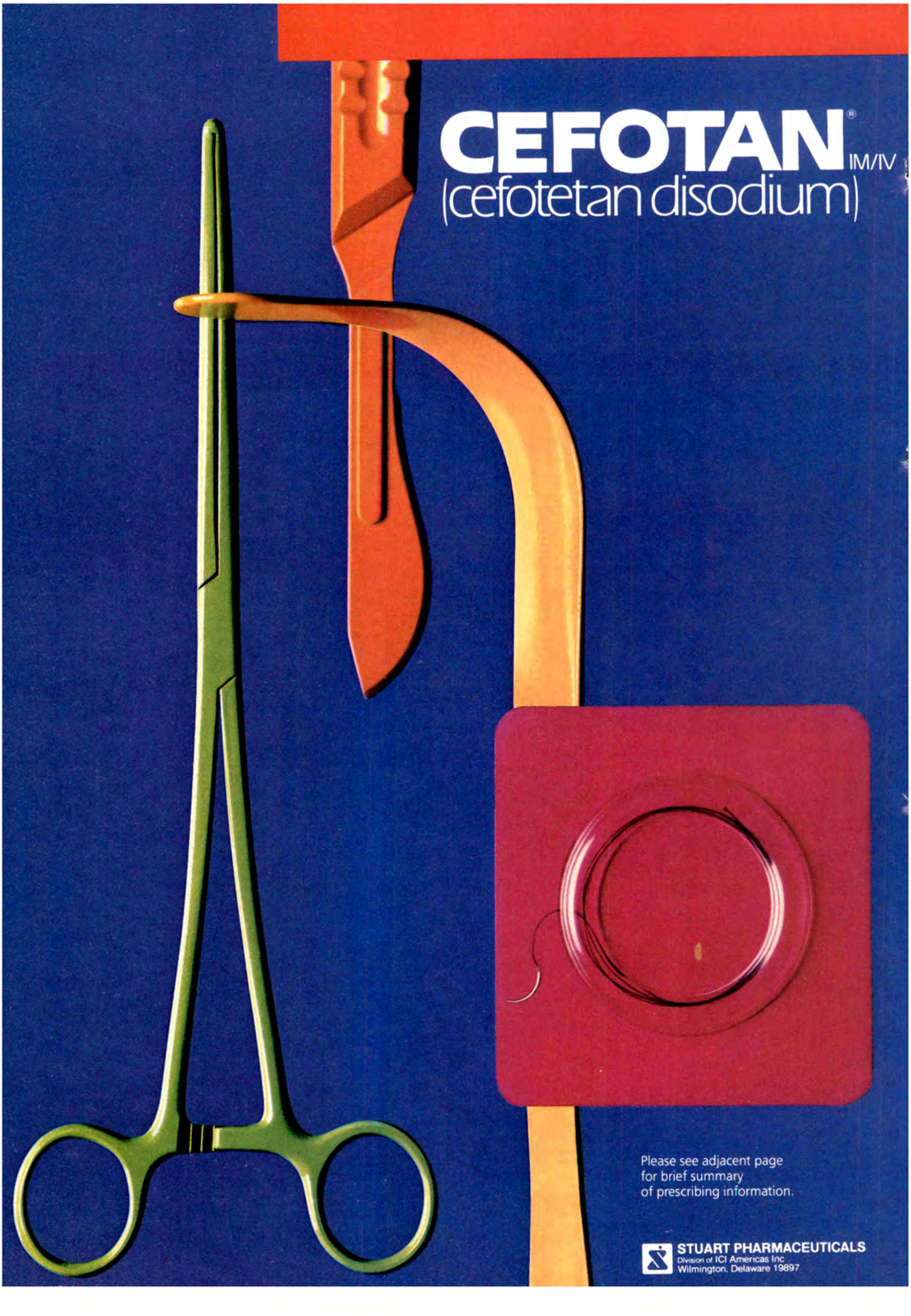

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Lower respiratory tract infections caused by *Streptococcus pneumoniae* (formerly *D pneumoniae*), *Staphylococcus aureus* (penicillinase- and nonpenicillinase-producing strains), *Haemophilus influenzae* (including ampicillin-resistant strains), *Klebsiella* species (including *K pneumoniae*), and *E coli*.

Skin and skin structure infections caused by *Staphylococcus aureus* (penicillinase- and nonpenicillinase-producing strains), *Staphylococcus epidermidis*,* *Streptococcus pyogenes* and *Streptococcus* species (excluding enterococci), and *E coli*.

Gynecologic infections caused by *Staphylococcus aureus*† (including penicillinase- and nonpenicillinase-producing strains), *Staphylococcus epidermidis*,* *Streptococcus* species (excluding enterococci), *E coli*, *Proteus mirabilis*, *Neisseria gonorrhoeae*, *Bacteroides* species (excluding *B distasonis*, *B ovatus*, *B thetaiotaomicron*), *Fusobacterium* species,† and gram-positive anaerobic cocci (including *Peptococcus* and *Peptostreptococcus* species†).

Intra-abdominal infections caused by *E coli*, *Klebsiella* species (including *K pneumoniae*†), *Streptococcus* species (excluding enterococci), and *Bacteroides* species (excluding *B distasonis*, *B ovatus*, *B thetaiotaomicron*).

Bone and joint infections caused by *Staphylococcus aureus*.†

***NOTE:** Some strains of *Staphylococcus epidermidis* are resistant to cefotetan.

†Efficacy for this organism in this organ system was studied in fewer than ten infections.

PROPHYLAXIS: The preoperative administration of CEFOTAN may reduce the incidence of certain postoperative infections in patients undergoing surgical procedures that are classified as clean contaminated or potentially contaminated (eg, cesarean section, abdominal or vaginal hysterectomy, transurethral surgery, biliary tract surgery, and gastrointestinal surgery).

The prophylactic dose of CEFOTAN should be administered 30 to 60 minutes prior to surgery. In patients undergoing cesarean section, CEFOTAN should be administered intravenously after the clamping of the umbilical cord.

If there are signs and symptoms of infection, specimens for culture should be obtained for identification of the causative organism so that appropriate therapeutic measures may be initiated.

CONTRAINDICATIONS
CEFOTAN is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

WARNINGS
Before therapy with CEFOTAN is instituted, careful inquiry should be made to determine whether the patient has had previous hypersensitivity reactions to cefotetan disodium, cephalosporins, penicillins, or other drugs. This product should be given cautiously to penicillin-sensitive patients. Antibiotics should be administered with caution to any patient who has demonstrated some form of allergy, particularly to drugs. If an allergic reaction to CEFOTAN occurs, discontinue the drug. Serious acute hypersensitivity reactions may require epinephrine and other emergency measures.

Pseudomembranous colitis has been reported with the use of cephalosporins (and other broad-spectrum antibiotics); therefore, it is important to consider its diagnosis in patients who develop diarrhea in association with antibiotic use.

Treatment with broad-spectrum antibiotics may alter normal flora of the colon and may permit overgrowth of clostridia. Studies indicate a toxin produced by *Clostridium difficile* is one primary cause of antibiotic-associated colitis. Cholestyramine and colestipol resins have been shown to bind the toxin in vitro.

Mild cases of colitis may respond to drug discontinuance alone. Moderate to severe cases should be managed with fluid, electrolyte, and protein supplementation as indicated. When the colitis is not relieved by drug discontinuance, or when it is severe, oral vancomycin is the treatment of choice for antibiotic-associated pseudomembranous colitis produced by *C difficile*. Other causes should also be considered.

PRECAUTIONS
GENERAL: As with other broad-spectrum antibiotics, prolonged use of CEFOTAN may result in overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection does occur during therapy, appropriate measures should be taken.

In common with many other broad-spectrum antibiotics, CEFOTAN may be associated with a fall in prothrombin activity. Those at risk include patients with renal or hepatic impairment, or poor nutritional state. Prothrombin times should be monitored in patients at risk and exogenous Vitamin K administered as indicated.

CEFOTAN should be used with caution in individuals with a history of gastrointestinal disease, particularly colitis.

INFORMATION FOR PATIENTS: As with some other cephalosporins, a disulfiram-like reaction characterized by flushing, sweating, headache, and tachycardia may occur when alcohol (beer, wine, etc) is ingested within 72 hours after CEFOTAN administration. Patients should be cautioned about the ingestion of alcoholic beverages following the administration of CEFOTAN.

DRUG INTERACTIONS: If CEFOTAN and an aminoglycoside are used concomitantly, renal function should be carefully monitored, especially if higher dosages of the aminoglycoside are to be administered or if therapy is prolonged, because of the potential nephrotoxicity and ototoxicity of aminoglycoside antibiotics. Although, to date, nephrotoxicity has not been noted when CEFOTAN was given alone, it is possible that nephrotoxicity may be potentiated if CEFOTAN is used concomitantly with an aminoglycoside.

DRUG/LABORATORY TEST INTERACTIONS: A false positive reaction for glucose in urine may occur with Benedict's or Fehling's solution.

As with other cephalosporins, high concentrations of cefotetan may interfere with measurement of serum and urine creatinine levels of Jaffe reaction and produce false increases in the levels of creatinine reported.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY: Although long-term studies in animals have not been performed to evaluate carcinogenic potential, no mutagenic potential of cefotetan was found in standard laboratory tests.

Cefotetan has adverse effects on the testes of prepubertal rats. Subcutaneous administration of

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developmentally analogous to late childhood and prepuberty in humans) resulted in reduced testicular weight and seminiferous tubule degeneration in 10 of 10 animals. Affected cells included spermatogonia and spermatocytes; Sertoli and Leydig cells were unaffected. Incidence and severity of lesions were dose-dependent; at 120 mg/kg/day (approx 2-4 times the usual human dose), only 1 of 10 treated animals was affected, and the degree of degeneration was mild. Similar lesions have been observed in experiments of comparable design with other methylthiotetrazole-containing antibiotics and impaired fertility has been reported, particularly at high dose levels. No testicular effects were observed in 7-week-old rats treated with up to 1000 mg/kg/day SC for 5 weeks, or in infant dogs (3 weeks old) that received up to 300 mg/kg/day IV for 5 weeks. The relevance of these findings to humans is unknown.

USAGE IN PREGNANCY: Pregnancy Category B: Reproduction studies have been performed in rats and monkeys at doses up to 20 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to cefotetan. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

USAGE IN NURSING MOTHERS: Cefotetan is excreted in human milk in very low concentrations. Caution should be exercised when cefotetan is administered to a nursing woman.

PEDIATRIC USE: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS
In clinical studies the following adverse effects were considered related to CEFOTAN therapy.

Gastrointestinal symptoms occurred in 1.5 percent of patients; the most frequent were diarrhea (1 in 80) and nausea (1 in 700).

Hematologic laboratory abnormalities occurred in 1.4 percent of patients and included eosinophilia (1 in 200), positive direct Coombs' test (1 in 250), and thrombocytosis (1 in 300).

Hepatic enzyme elevations occurred in 1.2 percent of patients and included a rise in SGPT (1 in 150), SGOT (1 in 300), alkaline phosphatase (1 in 700), and LDH (1 in 700).

Hypersensitivity reactions were reported in 1.2 percent of patients and included rash (1 in 150) and itching (1 in 700).

Local effects were reported in less than one percent of patients and included phlebitis at the site of injection (1 in 300), and discomfort (1 in 500).

DOSAGE AND ADMINISTRATION
TREATMENT: The usual adult dosage is 1 or 2 grams of CEFOTAN administered intravenously or intramuscularly every 12 hours for 5 to 10 days. Proper dosage and route of administration should be determined by the condition of the patient, severity of the infection, and susceptibility of the causative organism.

GENERAL GUIDELINES FOR DOSAGE OF CEFOTAN

Type of Infection	Daily Dose	Frequency and Route
Urinary Tract	1-4 grams	500 mg every 12 hours IV or IM 1 or 2 g every 24 hours IV or IM 1 or 2 g every 12 hours IV or IM
Other Sites	2-4 grams	1 or 2 g every 12 hours IV or IM
Severe	4 grams	2 g every 12 hours IV
Life-Threatening	6* grams	3 g every 12 hours IV

*Maximum daily dosage should not exceed 6 grams.

PROPHYLAXIS: To prevent postoperative infection in clean contaminated or potentially contaminated surgery in adults, the recommended dosage is 1 or 2 g of CEFOTAN administered once, intravenously, 30 to 60 minutes prior to surgery. In patients undergoing cesarean section, the dose should be administered as soon as the umbilical cord is clamped.

IMPAIRED RENAL FUNCTION: When renal function is impaired, a reduced dosage schedule must be employed. The following dosage guidelines may be used.

DOSAGE GUIDELINES FOR PATIENTS WITH IMPAIRED RENAL FUNCTION

Creatinine Clearance mL/min	Dose	Frequency
>30	Usual Recommended Dose*	Every 12 hours
10-30	Usual Recommended Dose*	Every 24 hours
<10	Usual Recommended Dose*	Every 48 hours

*Dose determined by the type and severity of infection, and susceptibility of the causative organism.

Cefotetan is dialyzable and it is recommended that for patients undergoing intermittent hemodialysis, one-quarter of the usual recommended dose be given every 24 hours on days between dialysis and one-half the usual recommended dose on the day of dialysis.

HOW SUPPLIED
CEFOTAN is a dry, white to pale yellow powder supplied in vials containing cefotetan disodium equivalent to 1 g and 2 g cefotetan activity for intravenous and intramuscular administration. The 1 g dose is available in 10 mL and 100 mL vials, and the 2 g dose is available in 20 mL and 100 mL vials. The vials should not be stored at temperatures above 22°C and should be protected from light.
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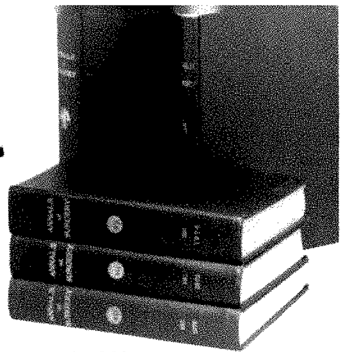

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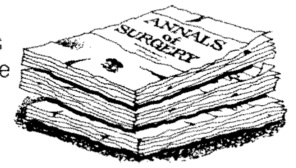

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Acute Abdominal Conditions: The administration of narcotics may obscure the diagnosis or clinical course of patients with acute abdominal conditions.

PRECAUTIONS

Special Risk Patients: VICODIN should be used with caution in elderly or debilitated patients and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, prostatic hypertrophy or urethral stricture.

Information for Patients: VICODIN, like all narcotics, may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery; patients should be cautioned accordingly.

Cough Reflex: Hydrocodone suppresses the cough reflex; caution should be exercised when VICODIN is used postoperatively and in patients with pulmonary disease.

Drug Interactions: The CNS-depressant effects of VICODIN may be additive with that of other CNS depressants. When combined therapy is contemplated, the dose of one or both agents should be reduced. The use of MAO inhibitors or tricyclic antidepressants with hydrocodone preparations may increase the effect of either the antidepressant or hydrocodone. The concurrent use of anticholinergics with hydrocodone may produce paralytic ileus.

Usage in Pregnancy: Pregnancy Category C. Hydrocodone has been shown to be teratogenic in hamsters when given in doses 700 times the human dose. There are no adequate and well-controlled studies in pregnant women. VICODIN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

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Nursing Mothers: It is not known whether this drug is excreted in human milk; therefore, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Central Nervous System: Sedation, drowsiness, mental clouding, lethargy, impairment of mental and physical performance, anxiety, fear, dysphoria, dizziness, psychic dependence, mood changes.

Gastrointestinal System: Nausea and vomiting may occur; they are more frequent in ambulatory than in recumbent patients. Prolonged administration of VICODIN may produce constipation.

Genitourinary System: Ureteral spasm, spasm of vesical sphincters and urinary retention have been reported.

Respiratory Depression: (See WARNINGS.)

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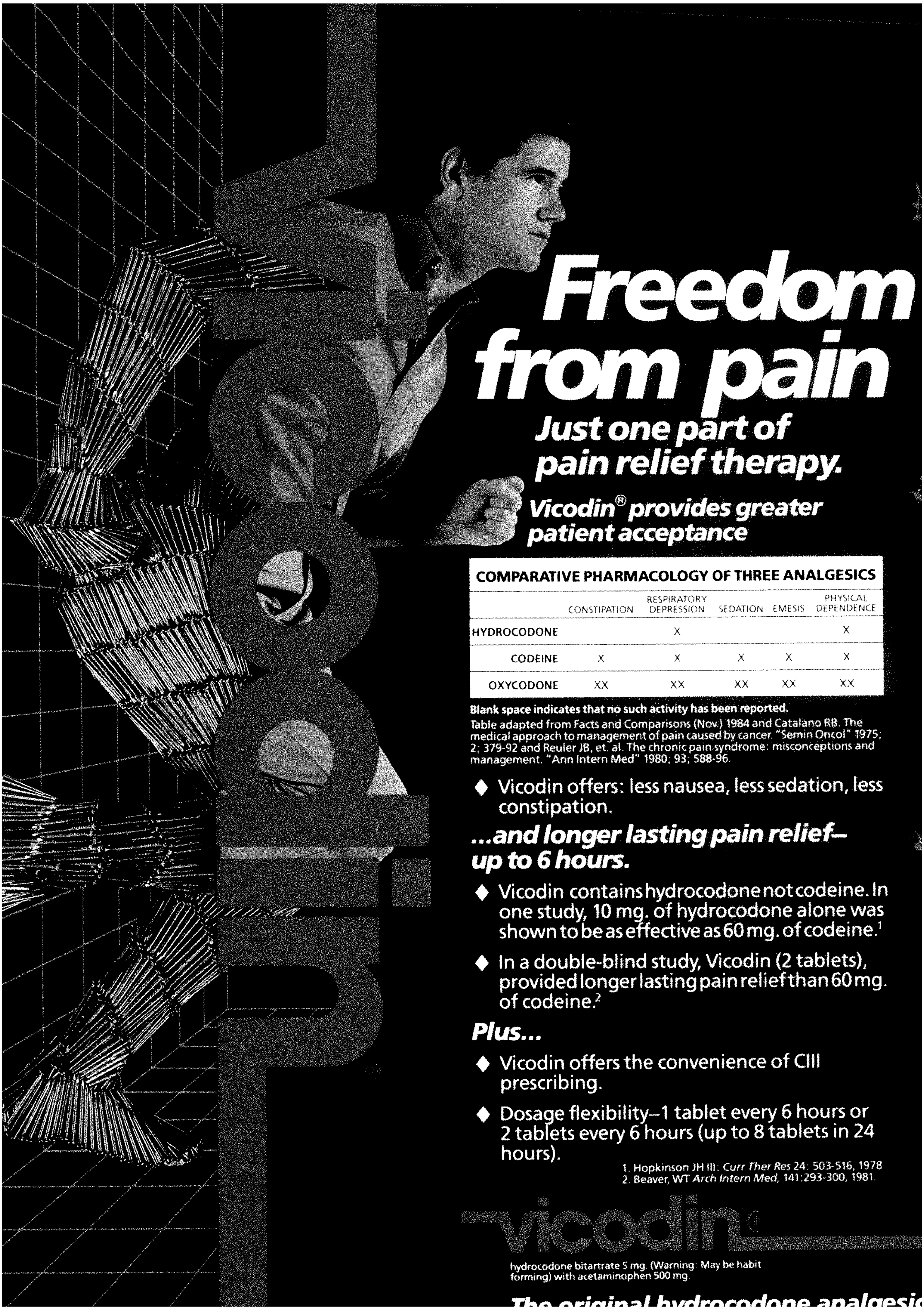

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CODEINE	X	X	X	X	X
OXYCODONE	XX	XX	XX	XX	XX

Blank space indicates that no such activity has been reported.

Table adapted from Facts and Comparisons (Nov.) 1984 and Catalano RB. The medical approach to management of pain caused by cancer. "Semin Oncol" 1975; 2; 379-92 and Reuler JB, et. al. The chronic pain syndrome: misconceptions and management. "Ann Intern Med" 1980; 93; 588-96.

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1. Hopkinson JH III: *Curr Ther Res* 24: 503-516, 1978
2. Beaver, WT *Arch Intern Med*, 141:293-300, 1981.

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Before prescribing, please see full prescribing information. A Brief Summary follows:

Thrombostat must not be injected! Apply on the surface of bleeding tissue as a solution or powder.

INDICATIONS AND USAGE: Thrombostat (Thrombin, USP) is indicated as an aid in hemostasis wherever oozing blood from capillaries and small venules is accessible.

In various types of surgery solutions of Thrombostat may be used in conjunction with Absorbable Gelatin Sponge, USP for hemostasis.

CONTRAINDICATIONS: Thrombostat is contraindicated in persons known to be sensitive to any of its components and/or to material of bovine origin.

WARNING: Because of its action in the clotting mechanism, Thrombostat must not be injected or otherwise allowed to enter large blood vessels. Extensive intravascular clotting and even death may result. Thrombostat is an antigenic substance and has caused sensitivity and allergic reactions when injected into animals.

PRECAUTIONS: General: Consult the absorbable gelatin sponge product labeling for complete information for use prior to utilizing the thrombin-saturated-sponge procedure.

Pregnancy—Teratogenic effects: Pregnancy Category C. Animal reproduction studies have not been conducted with Thrombin, Topical (Bovine). It is also not known whether Thrombin, Topical (Bovine) can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Thrombin, Topical (Bovine) should be given to a pregnant woman only if clearly indicated.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: An allergic type reaction following the use of Thrombostat for treatment of epistaxis has been reported. Febrile reactions have also been observed following the use of Thrombostat in certain surgical procedures but no cause-effect relationship has been established.

DOSAGE AND ADMINISTRATION: General: Solutions of Thrombostat may be prepared in sterile distilled water or isotonic saline. The intended use determines the strength of the solution to prepare. For general use in plastic surgery, dental extractions, skin grafting, neurosurgery, etc. solutions containing approximately 100 units per ml are frequently used. For this, 10 ml of diluent added to the 1000 unit package is suitable. Where bleeding is profuse, as from cut surfaces of liver and spleen, concentrations as high as 1000 to 2000 units per ml may be required. For this the 5000 unit vial dissolved in 5 ml or 2.5 ml respectively, of the diluent supplied in the package is convenient. Intermediate strengths to suit the needs of the case may be prepared by selecting the proper strength package and dissolving the contents in an appropriate volume of diluent. In many situations, it may be advantageous to use Thrombostat (Thrombin, USP) in dry form on oozing surfaces.

Caution: Solutions should be used the day they are prepared. The solution may be used for up to 6 hours when stored at room temperature; up to 24 hours when stored under refrigeration, and, if necessary, up to 48 hours when stored frozen.

The following techniques are suggested for the topical application of Thrombostat.

1. The recipient surface should be sponged (not wiped) free of blood before Thrombostat is applied.
2. A spray may be used or the surface may be flooded using a sterile syringe and small gauge needle. The most effective hemostasis results when the Thrombostat mixes freely with the blood as soon as it reaches the surface.
3. In instances where Thrombostat in dry form is needed, the vial is opened by removing the metal ring by flipping up the plastic cap and tearing counterclockwise. The rubber-diaphragm cap may be easily removed and the dried Thrombostat is then broken up into a powder by means of a sterile glass rod or other suitable sterile instrument.
4. Sponging of treated surfaces should be avoided in order that the clot remain securely in place.

Thrombostat may be used in conjunction with Absorbable Gelatin Sponge, USP as follows:

1. Prepare Thrombostat solution of the desired strength.
2. Immerse sponge strips of the desired size in the Thrombostat solution. Knead the sponge strips vigorously with moistened gloved fingers to remove trapped air, thereby facilitating saturation of the sponge.
3. Apply saturated sponge to bleeding area. Hold in place for 10 to 15 seconds with a pledget of cotton or a small gauze sponge.

Thrombostat Kit: Thrombostat Kit contains one sterile 20,000 unit vial of Thrombostat, one sterile vial of Isotonic Saline Diluent, and one sterile pump sprayer cap. The Kit may be used as follows:

1. Remove the Tyvek blister lid by pulling up at the indicated corner. The sterile inner tray can be lifted out or introduced into the operating field.
2. The cover to the sterile inner tray is removed by pulling up on the finger tab, exposing the sterile contents.
3. Thrombostat solution of the desired strength is prepared and the pump sprayer cap inserted and seated on the Thrombostat solution vial. Note: Several strokes of the pump sprayer will be required before the Thrombostat solution is expelled.
4. Alternatively, when Thrombostat in dry form is needed, the vial is opened as described above and the dried Thrombostat broken up into a powder by means of a sterile glass rod or other suitable sterile instrument.

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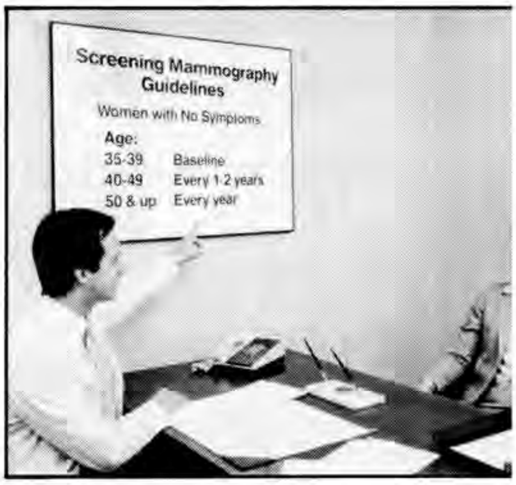

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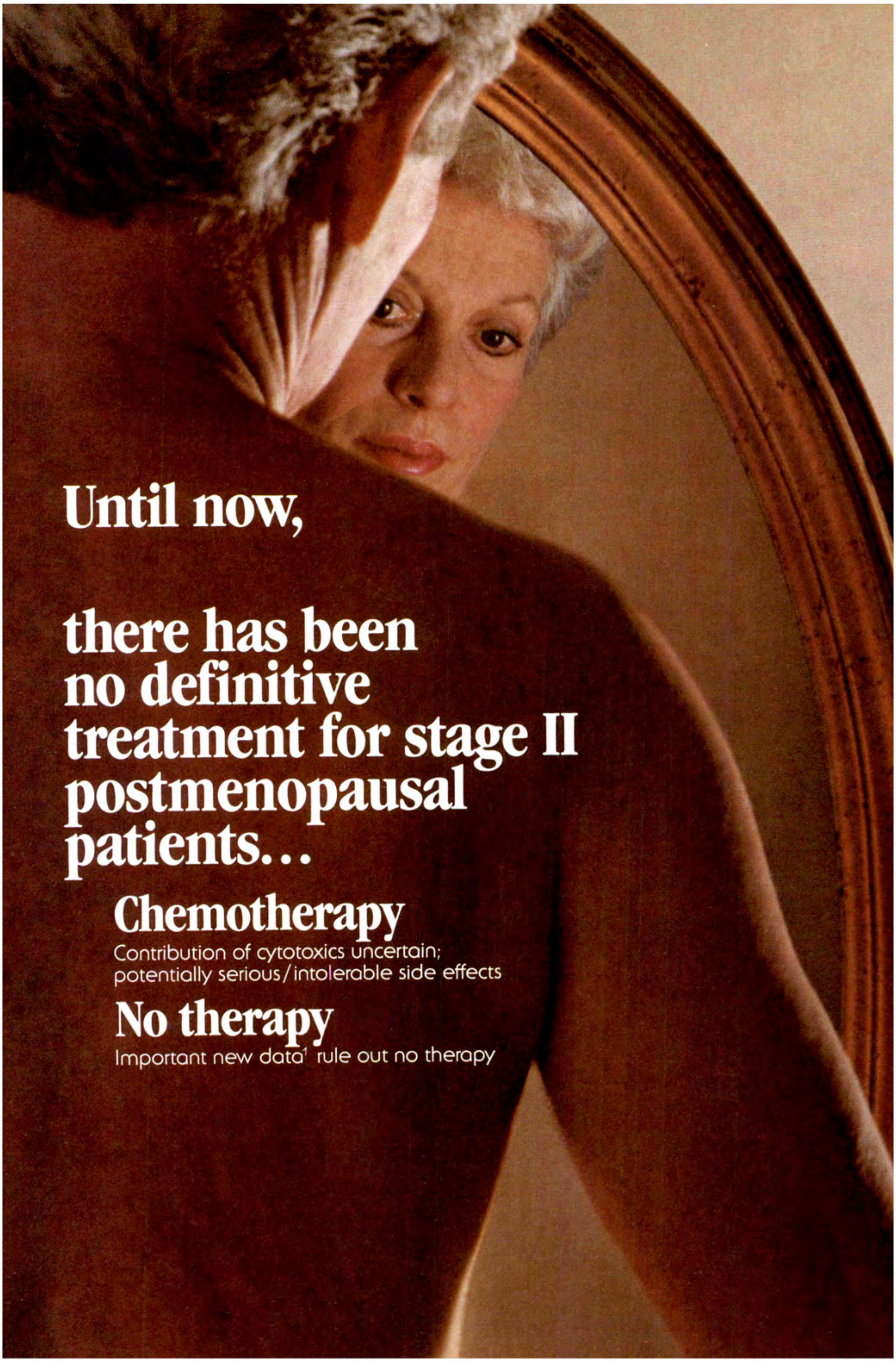
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A recent National Institutes of Health consensus report states that following surgery, "Tamoxifen [NOLVADEX] should now be regarded as standard therapy for postmenopausal patients with positive axillary lymph nodes and positive hormone receptor status."[1]

NOLVADEX increases disease-free time[2-5] by delaying recurrence following total mastectomy and axillary dissection in postmenopausal women with breast cancer ($T_{1\text{-}3}$, N_1, M_0). Moreover, NOLVADEX improves overall survival, with a 34% reduction in risk of mortality, as observed in the NOLVADEX Adjuvant Trial Organization (NATO) study.[4] This treatment is extremely well tolerated by patients[2-5]; in fact, one double-blind, placebo-controlled study demonstrated a NOLVADEX side effects profile similar to placebo.[2] And, since NOLVADEX has a mild side effects profile and is easy to administer, patients are afforded a better quality of life. NOLVADEX—today's promising breast cancer therapy for the postmenopausal woman—in the adjuvant setting and in metastatic disease.

Please see next page for brief summary of prescribing information.

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10 MG TABLETS

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BRIEF SUMMARY

INDICATIONS AND USAGE: NOLVADEX is effective in the treatment of metastatic breast cancer in postmenopausal women. Available evidence indicates that patients whose tumors are estrogen receptor positive are more likely to benefit from NOLVADEX therapy.

NOLVADEX is effective in delaying recurrence following total mastectomy and axillary dissection in postmenopausal women with breast cancer (T1-3, N1, M0). The estrogen and progesterone receptor values may help to predict whether NOLVADEX therapy is likely to be beneficial. In some NOLVADEX adjuvant studies, most of the benefit to date has been in the subgroup with 4 or more positive axillary nodes.

CONTRAINDICATIONS: None known.

WARNINGS: Pregnancy Category D: NOLVADEX may cause fetal harm when administered to a pregnant woman. Individuals should not become pregnant while taking NOLVADEX. Effects on reproductive functions are expected from the antiestrogenic properties of the drug. In reproductive studies in rats at dose levels equal to or below the human dose, nonteratogenic developmental skeletal changes were seen and were found to be reversible. In addition, in fertility studies in rats and in teratology studies in rabbits using doses at or below those used in humans, a lower incidence of embryo implantation and a higher incidence of fetal death or retarded in utero growth were observed, with slower learning behavior in some rat pups. The impairment of learning behavior did not achieve statistical significance in one study, and, in another study where significance was reported, this was by comparing dosed animals with controls of another study. Several pregnant marmosets were dosed during organogenesis or in the last half of pregnancy. No deformations were seen and, although the dose was high enough to terminate pregnancy in some animals, those that did maintain pregnancy showed no evidence of teratogenic malformations. There are no adequate and well controlled studies in pregnant women. There have been reports of spontaneous abortions, birth defects, fetal deaths, and vaginal bleeding. If this drug is used during pregnancy or the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

Ocular changes have been reported in a few patients who, as part of a clinical trial, were treated for periods greater than one year with NOLVADEX at doses at least four times the highest recommended daily dose of 40 mg. The ocular changes consist of retinopathy and, in some patients, there are also corneal changes and a decrease in visual acuity.

In addition, a few cases of ocular changes including visual disturbance, corneal changes, and/or retinopathy have been reported in patients treated with NOLVADEX at recommended doses. It is uncertain if these effects are due to NOLVADEX.

As with other additive hormonal therapy (estrogens and androgens), hypercalcemia has been reported in some breast cancer patients with bone metastases within a few weeks of starting treatment with NOLVADEX. If hypercalcemia does occur, appropriate measures should be taken and, if severe, NOLVADEX should be discontinued.

PRECAUTIONS: General: NOLVADEX should be used cautiously in patients with existing leukopenia or thrombocytopenia. Observations of leukopenia and thrombocytopenia occasionally have been made, but it is uncertain if these effects are due to NOLVADEX therapy. Transient decreases in platelet counts, usually to 50,000-100,000/cu mm, infrequently lower, have been occasionally reported in patients taking NOLVADEX for breast cancer. No hemorrhagic tendency has been recorded and the platelet counts returned to normal levels even though treatment with NOLVADEX continued.

Laboratory Tests: Periodic complete blood counts, including platelet counts, may be appropriate.

Carcinogenesis: While no conventional bioassay has been conducted, endocrine changes in immature and mature mice were investigated in a 13-month study. Granulosa cell ovarian tumors and interstitial cell testicular tumors were found in mice receiving NOLVADEX, but not in the controls.

Mutagenesis: No genotoxic potential has been found in a battery of in vivo and in vitro tests with pro- and eukaryotic test systems with drug metabolizing systems present.

Impairment of Fertility: Fertility in female rats was decreased following administration of 0.04 mg/kg for 2 weeks prior to mating through day 7 of pregnancy. There was a decreased number of implantations, and all fetuses were found dead.

Following administration to rats of 0.16 mg/kg from days 7-17 of pregnancy, there were increased numbers of fetal deaths. Administration of 0.125 mg/kg to rabbits during days 6-18 of pregnancy resulted in abortion or premature delivery. Fetal deaths occurred at higher doses. There were no teratogenic changes in either rat or rabbit segment II studies. Several pregnant marmosets were dosed with 10 mg/kg/day either during organogenesis or in the last half of pregnancy. No deformations were seen, and, although the dose was high enough to terminate pregnancy in some animals, those that did maintain pregnancy showed no evidence of teratogenic malformations. Rats given 0.16 mg/kg from day 17 of pregnancy to 1 day before weaning demonstrated increased numbers of dead pups at parturition. It was reported that some rat pups showed slower learning behavior, but this did not achieve statistical significance in one study, and in another study where significance was reported, this was by comparing dosed animals with controls of another study.

The recommended daily human dose of 20-40 mg corresponds to 0.4-0.8 mg/kg for an average 50 kg woman.

Pregnancy Category D: See WARNINGS.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from NOLVADEX, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

ADVERSE REACTIONS: The most frequent adverse reactions to NOLVADEX are hot flashes, nausea and vomiting. These may occur in up to one fourth of patients, but are rarely severe enough to require discontinuation of treatment.

Less frequently reported adverse reactions are vaginal bleeding, vaginal discharge, menstrual irregularities and skin rash. Usually these have not been of sufficient severity to require dosage reduction or discontinuation of treatment.

Increased bone and tumor pain and, also, local disease flare have occurred, which are sometimes associated with a good tumor response. Patients with increased bone pain may require additional analgesics. Patients with soft tissue disease may have sudden increases in the size of preexisting lesions, sometimes associated with marked erythema within and surrounding the lesions and/or the development of new lesions. When they occur, the bone pain or disease flare are seen shortly after starting NOLVADEX and generally subside rapidly.

Other adverse reactions which are seen infrequently are hypercalcemia, peripheral edema, distaste for food, pruritus vulvae, depression, dizziness, light-headedness and headache. There have been infrequent reports of thromboembolic events occurring during NOLVADEX therapy. Since for cancer patients in general an increased incidence of thromboembolic events is known to occur, a causal relationship to NOLVADEX remains conjectural. An increased incidence has been reported when cytotoxins are combined with NOLVADEX.

If adverse reactions are severe, it is sometimes possible to control them by a simple reduction of dosage without loss of control of the disease.

OVERDOSAGE: Acute overdosage in humans has not been reported. Signs observed at the highest doses following studies to determine LD_{50} in animals were respiratory difficulties and convulsions. No specific treatment for overdosage is known; treatment must be symptomatic.

DOSAGE AND ADMINISTRATION: One or two 10 mg tablets twice a day (morning and evening). In the three single agent adjuvant NOLVADEX studies noted above (See Clinical Pharmacology), NOLVADEX was administered for two years. The optimal duration of adjuvant therapy is not known.

HOW SUPPLIED: Tablets containing tamoxifen as the citrate in an amount equivalent to 10 mg of tamoxifen (round, biconvex, uncoated, white tablet identified with NOLVADEX 600 debossed on one side and a cameo debossed on the other side) are supplied in bottles of 60 tablets and 250 tablets. Protect from heat and light.

NDC 0310-0600

Rev. 1/2/87

ICI PHARMA

Division of ICI Americas Inc
WILMINGTON, DELAWARE 19897 USA

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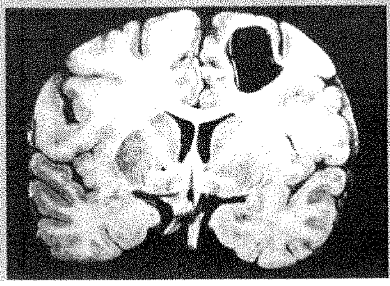
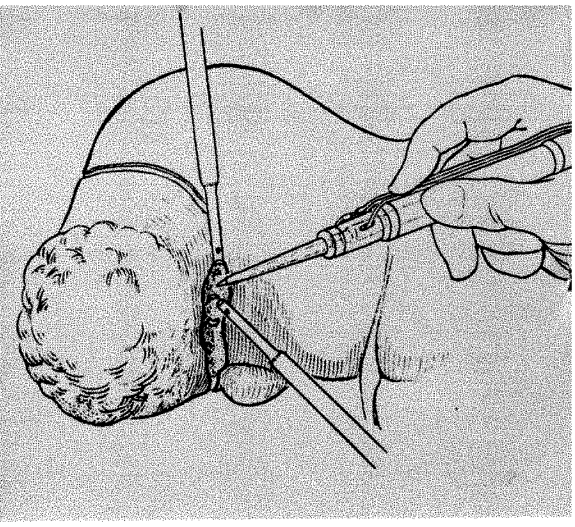
Now...the new book that shows you the role of surgical resection in the curative treatment of metastatic cancer



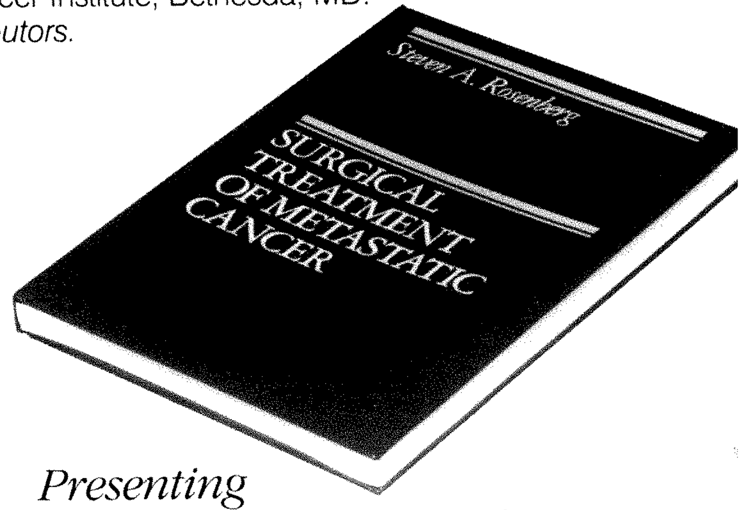


SURGICAL TREATMENT of METASTATIC CANCER

Edited by Steven A. Rosenberg, M.D., Ph.D.

Chief of Surgery, National Cancer Institute, Bethesda, MD.
9 contributors.

> *For many patients with isolated visceral metastases from solid tumors, surgical resection of those metastatic deposits represents the best opportunity for cure. For patients with solitary pulmonary and hepatic metastases, up to 30% of patients may experience prolonged disease-free survival after metastasectomy. Only a small subset of patients with metastatic cancer are likely to benefit from surgical resection and identification of these patients is an important part of the application of this treatment.*
>
> **—from the *Preface***



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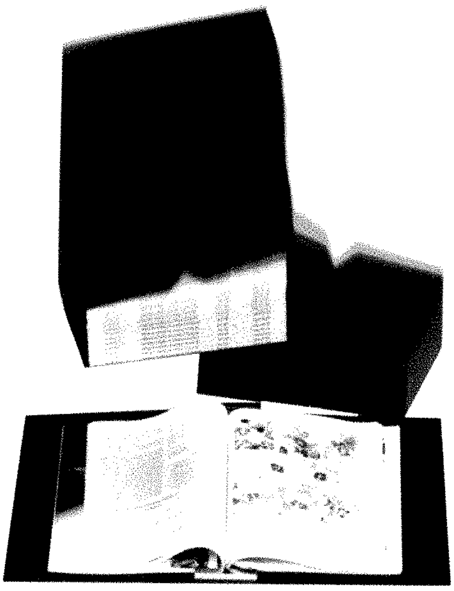

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NUBAIN IM IV SC
nalbuphine HCl

Brief Summary of Prescribing Information

INDICATIONS For the relief of moderate to severe pain. NUBAIN can also be used for preoperative analgesia, as a supplement to surgical anesthesia, and for obstetrical analgesia during labor.

CONTRAINDICATIONS NUBAIN should not be administered to patients who are hypersensitive to it.

WARNINGS Drug Dependence NUBAIN has been shown to have a low abuse potential which is approximate to that of pentazocine. When compared with drugs which are not mixed agonist-antagonists, it has been reported that nalbuphine's potential for abuse would be less than that of codeine and propoxyphene. Psychological and physical dependence and tolerance may follow the abuse or misuse of nalbuphine. Therefore, caution should be observed in prescribing it for emotionally unstable patients, or for individuals with a history of narcotic abuse. Such patients should be closely supervised when long-term therapy is contemplated. Care should be taken to avoid increases in dosage or frequency of administration which in susceptible individuals might result in physical dependence. Abrupt discontinuation of NUBAIN following prolonged use has been followed by symptoms of narcotic withdrawal, i.e., abdominal cramps, nausea and vomiting, rhinorrhea, lacrimation, restlessness, anxiety, elevated temperature and piloerection. **Use in Ambulatory Patients** NUBAIN may impair the mental or physical abilities required for the performance of potentially dangerous tasks such as driving a car or operating machinery. Therefore, NUBAIN should be administered with caution to ambulatory patients who should be warned to avoid such hazards. **Use in Emergency Procedures** Maintain patient under observation until recovered from NUBAIN effects that would affect driving or other potentially dangerous tasks. **Use in Children** Clinical experience to support administration to patients under 18 years is not available at present. **Use in Pregnancy (other than labor)** Safe use of NUBAIN in pregnancy has not been established. Although animal reproductive studies have not revealed teratogenic or embryotoxic effects, nalbuphine should only be administered to pregnant women when, in the judgement of the physician, the potential benefits outweigh the possible hazards. **Use During Labor and Delivery** NUBAIN can produce respiratory depression in the neonate. It should be used with caution in women delivering premature infants. **Head Injury and Increased Intracranial Pressure** The possible respiratory depressant effects and the potential of potent analgesics to elevate cerebrospinal fluid pressure (resulting from vasodilation following CO_2 retention) may be markedly exaggerated in the presence of head injury, intracranial lesions or a pre-existing increase in intracranial pressure. Furthermore, potent analgesics can produce effects which may obscure the clinical course of patients with head injuries. Therefore, NUBAIN should be used in these circumstances only when essential, and then should be administered with extreme caution. **Interaction With Other Central Nervous System Depressants** Although NUBAIN possesses narcotic antagonist activity, there is evidence that in nondependent patients it will not antagonize a narcotic analgesic administered just before, concurrently, or just after an injection of NUBAIN. Therefore, patients receiving a narcotic analgesic, general anesthetics, phenothiazines, or other tranquilizers, sedatives, hypnotics, or other CNS depressants (including alcohol) concomitantly with NUBAIN may exhibit an additive effect. When such combined therapy is contemplated, the dose of one or both agents should be reduced. **Sulfites Sensitivity** NUBAIN contains sodium metabisulfite, a sulfite that may cause allergic-type reactions (e.g., hives, itching, wheezing, anaphylaxis) in certain susceptible persons. Although the overall prevalence of sulfite sensitivity in the general population is probably low, it is seen more frequently in asthmatics or in atopic nonasthmatic persons.

PRECAUTIONS Impaired Respiration At the usual adult dose of 10 mg/70 kg, NUBAIN causes some respiratory depression approximately equal to that produced by equal doses of morphine. However, in contrast to morphine, respiratory depression is not appreciably increased with higher doses of NUBAIN. Respiratory depression induced by NUBAIN can be reversed by NARCAN® (naloxone hydrochloride) when indicated. NUBAIN should be administered with caution at low doses to patients with impaired respiration (e.g., from other medication, uremia, bronchial asthma, severe infection, cyanosis or respiratory obstructions). **Impaired Renal or Hepatic Function** Because NUBAIN is metabolized in the liver and excreted by the kidneys, patients with renal or liver dysfunction may overreact to customary doses. Therefore, in these individuals, NUBAIN should be used with caution and administered in reduced amounts. **Myocardial Infarction** As with all potent analgesics, NUBAIN should be used with caution in patients with myocardial infarction who have nausea or vomiting. **Biliary Tract Surgery** As with all narcotic analgesics, NUBAIN should be used with caution in patients about to undergo surgery of the biliary tract since it may cause spasm of the sphincter of Oddi.

ADVERSE REACTIONS The most frequent adverse reaction in 1066 patients treated with NUBAIN is sedation 381 (36%). Less frequent reactions are sweaty/clammy 99 (9%); nausea/vomiting 68 (6%); dizziness/vertigo 58 (5%); dry mouth 44 (4%); and headache 27 (3%). Other adverse reactions which may occur (reported incidence of 1% or less) are: **CNS Effects** Nervousness, depression, restlessness, crying, euphoria, floating, hostility, unusual dreams, confusion, faintness, hallucinations, dysphoria, feeling of heaviness, numbness, tingling, unreality. The incidence of psychotomimetic effects, such as unreality, depersonalization, delusions, dysphoria and hallucinations has been shown to be less than that which occurs with pentazocine. **Cardiovascular** Hypertension, hypotension, bradycardia, tachycardia. **Gastrointestinal** Cramps, dyspepsia, bitter taste. **Respiration** Depression, dyspnea, asthma. **Dermatological** Itching, burning, urticaria. **Miscellaneous** Speech difficulty, urinary urgency, blurred vision, flushing and warmth. **Patients Dependent on Narcotics** Patients who have been taking narcotics chronically may experience withdrawal symptoms upon the administration of NUBAIN. If unduly troublesome, narcotic withdrawal symptoms can be controlled by the slow intravenous administration of small increments of morphine, until relief occurs. If the previous analgesic was morphine, meperidine, codeine, or other narcotic with similar duration of activity, one-fourth of the anticipated dose of NUBAIN can be administered initially and the patient observed for signs of withdrawal, i.e., abdominal cramps, nausea and vomiting, lacrimation, rhinorrhea, anxiety, restlessness, elevation of temperature or piloerection. If untoward symptoms do not occur, progressively larger doses may be tried at appropriate intervals until the desired level of analgesia is obtained with NUBAIN. **Management of Overdosage** The immediate intravenous administration of NARCAN® (naloxone hydrochloride) is a specific antidote. Oxygen, intravenous fluids, vasopressors and other supportive measures should be used as indicated. The administration of single doses of 72 mg of NUBAIN subcutaneously to eight normal subjects has been reported to have resulted primarily in symptoms of sleepiness and mild dysphoria.

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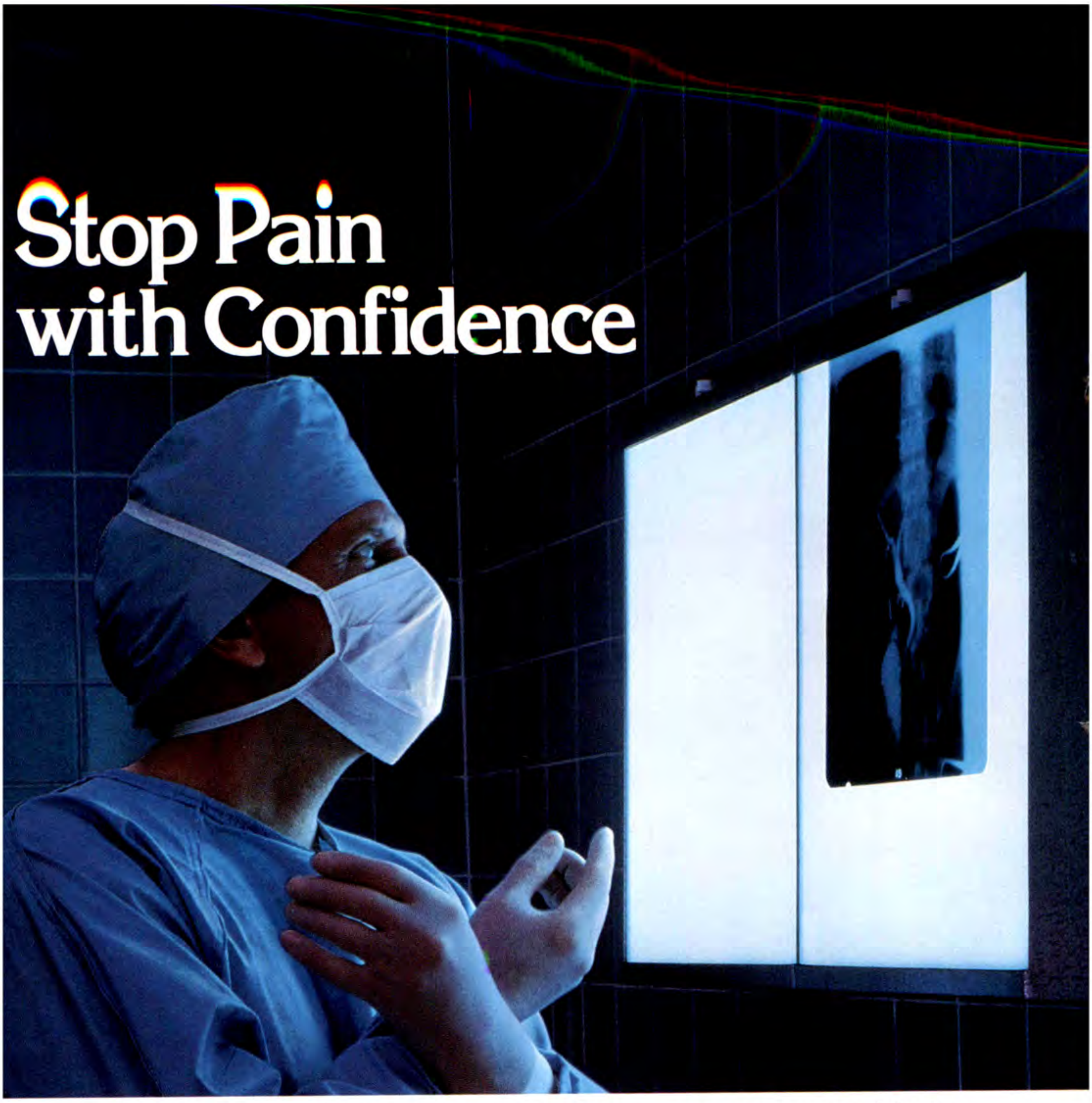

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Nutrition After Vertical Banded Gastroplasty

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The authors assessed the nutritional status of 60 morbidly obese patients by determining body composition, using multiple isotope dilution at 13.6 ± 0.4 months following operation. Body weight was followed for an additional 12.3 ± 0.8 months. Twenty-four patients lost more than 25% of their preoperative weight and were within 30% of ideal weight (a "good" result). At 1 year they had lost 41.4 ± 1.8% of preoperative weight and the body mass index (BMI) decreased from 46.7 ± 1.2 to 27.0 ± 0.6 kg/m^2. Despite rapid weight loss, malnutrition did not develop and their body composition became indistinguishable from that of normally nourished volunteers. Twenty-nine patients had a "satisfactory" result with more than 25% weight loss but were not within 30% of ideal. Their weight decreased by 34.8 ± 1.0% as their BMI decreased from 55.4 ± 1.2 to 36.0 ± 0.8 kg/m^2. Seven patients lost less than 25% of their preoperative weight (an "unsatisfactory" result). Malnutrition did not develop in any patient. In the authors' experience, in contrast to other weight reducing operations, vertical banded gastroplasty (VBG) results in rapid weight loss without the concomitant development of malnutrition even in patients who return to normal weight.

MALNUTRITION COMMONLY OCCURS in patients who have had significant weight loss following operations for morbid obesity.[1,2] The malnutrition that develops following jejunoileal bypass has been classified as kwashiorkor in type, as it is associated with hepatic dysfunction and is similar to what occurs with protein deprivation without carbohydrate restriction. These patients usually have a reduction in the plasma concentrations of essential amino acids, an elevation of plasma glycine, and a favorable therapeutic response either to intravenous amino acids or to restoration of intestinal continuity.[3,4]

In contrast, operations designed to limit intake result in a decreased intake of both calories and protein, and malnutrition more closely mimics marasmus, in which liver failure is rare but vitamin deficiencies are common.[1] Patients with malnutrition following intake-limiting procedures exhibit weakness, easy fatigue, a failure to return to their former occupation,[1] repeated infections and immunologic incompetence,[5] Wernicke-Korsakoff disease,[6] and vitamin B-12 and folic acid deficiencies. Nutritional studies of gastric limiting operations until now have been confined to gastric bypass or to horizontal gastroplasty. The malnutrition that develops following both jejunoileal bypass and gastric limiting operations is characterized by an abnormal contraction of the body cell mass (BCM) with an expansion of extracellular mass (ECM).[1,2]

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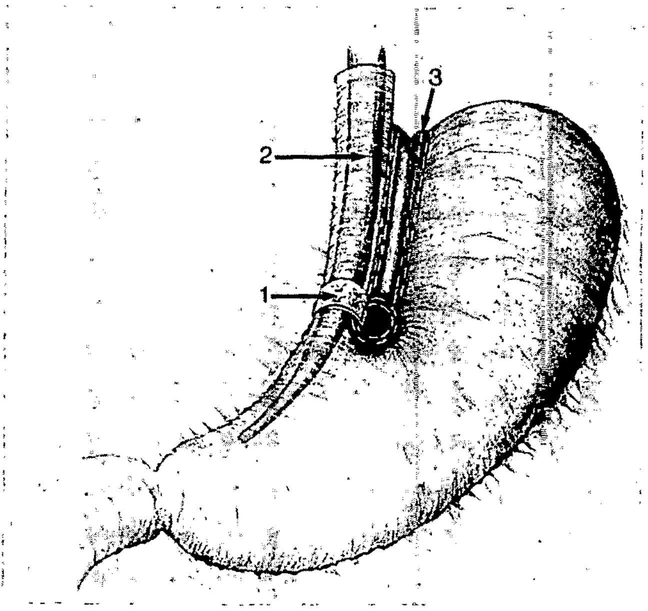


FIG. 1. Vertical banded gastroplasty (1) polypropylene band created an external circumference of outlet orifice of 55 mm in two patients, 50 mm in seven patients, and 41–45 mm in 51 patients; (2) 26 Fr bougie within new gastric pouch; and (3) vertical staple line.

In this study, we measured body composition by multiple isotope dilution in 60 patients 13.6 ± 0.4 months after vertical banded gastroplasty (VBG) to document the nutritional consequences of this popular operation for the control of morbid obesity. We followed the stability of weight loss by measuring weight change for an additional 12.3 ± 0.8 months following the measurement of body composition.

Materials and Methods

Patient Selection

All patients entered into the study were at least twice ideal weight, had a body mass index (BMI) of 50.7 ± 1.0 kg/m^2, and were considered capable of participating in an exacting postoperative follow-up program. After surgery all patients were seen weekly for 1 month, monthly for 1 year, and then bimonthly by a research dietitian, the surgical staff, and by a psychiatrist if necessary. Weight, height, and ideal weight[7] were recorded for each patient before and at the stated intervals after surgery.

Operative Procedure

We performed VBG on all 60 patients.[8] A single layer of polypropylene mesh was used to band the orifice of the proximal gastric pouch (Fig. 1). This material was cut 15 mm wide and 60–70 mm long and overlapped to create an external circumference of 55 mm in two patients, 50 mm in seven patients, and 41–45 mm in 51 patients. The material used for banding was sutured to itself and not to the gastric wall using 4 polypropylene sutures. A No. 26 Fr bougie was used as a guide to establish the size of the gastric pouch. We used two rows of 4.8 mm vertical staples in all patients.

Measurement of Body Composition

Body composition was determined by multiple isotope dilution[9] at a mean of 13.6 ± 0.4 months after surgery. These measurements involved the simultaneous intravenous injection of 8 μCi of sodium-22 and 500 μCi of tritiated water. The plasma isotope concentrations were determined at 4 and 24 hours following isotope injection. All of the urine and any extrarenal fluid lost during the 24-hour isotopic equilibration period were collected to correct for isotope loss. Total exchangeable sodium (Na_e) was determined from the equilibrated plasma sodium-22 specific activity at 24 hours. Total body water (TBW) was calculated from the equilibrated plasma tritium concentration at 24 hours. Total exchangeable potassium (K_e) was calculated from TBW, Na_e, and the ratio in whole blood of the sodium plus potassium content divided by its water content. Lean body mass (LBM), body fat, and BCM were calculated from equations previously published.[10] The Na_e/K_e ratio is a sensitive index of the nutritional state. In the normally nourished this ratio approximates unity with an upper 95% confidence limit of 1.22. Malnutrition is characterized by a loss of BCM, accompanied by an expansion of the ECM, and thus an increase in the Na_e/K_e ratio. Malnutrition was therefore defined by a Na_e/K_e ratio greater than 1.22.[9] Because many preoperative body composition measurements have been recorded in obese patients, only postoperative nutritional measurements were performed in this study. The postoperative body composition data were compared to similar data obtained in 25 normally nourished healthy volunteers and in 100 preoperative morbidly obese patients.

Evaluation

We performed endoscopy with an 11-mm endoscope at 6 weeks, 6 months, and 1 year following gastroplasty to determine stoma size and the continuity of the vertical staple line separating the new small stomach from the gastric fundus. An upper gastrointestinal x-ray series was also obtained to rule out staple line disruption at 1 year and repeated later if clinically indicated.

Patients were individually classified on the basis of weight loss as "good" (if the weight loss after operation exceeded 25% of preoperative weight and was within 30% of ideal weight), "satisfactory" (if weight loss exceeded 25% but the patient still exceeded 30% of ideal),

TABLE 1. *Nutritional Status Following Vertical Banded Gastroplasty (13.6 ± 0.4 Months)*

	Normal	Good	Satisfactory	Unsatisfactory
Controls				
Patients	25	24	29	7
Weight (Kg)	70.4 ± 2.5	72.4 ± 2.2*	96.5 ± 2.8	89.2 ± 5.3
Weight loss (%)		41.4 ± 1.8	34.8 ± 1.0	21.0 ± 0.9
Fat (Kg)	20.1 ± 1.4	23.4 ± 1.7*	39.4 ± 1.7	39.2 ± 3.2
Body cell mass (Kg)	24.6 ± 1.1	22.5 ± 1.2	25.4 ± 1.0	23.6 ± 1.6
Na_e/K_e	0.98 ± 0.02	1.09 ± 0.04	1.14 ± 0.03	1.03 ± 0.07
Vitamin B-12 (% normal)		92	93	100
Folate (% normal)		67	59	71
Iron (% normal)		91	66	71
Stoma (% <11 mm—with intact vertical staple line)		100	86	29

* $p < 0.05$ between good and both satisfactory and unsatisfactory.

and "unsatisfactory" (if the weight loss was less than 25% of preoperative weight). These patients were followed closely for weight change for an additional year (12.3 ± 0.8 months) following the body composition measurement. The patients also were classified at 13.6 ± 0.4 and 25.9 ± 0.8 months as excellent, good, fair, poor, or failure using the criteria of Reinhold.[11]

Assessment of Food Intake

Patients recorded their food intake over a 7-day period immediately prior to the measurement of body composition. Types and quantities of foods consumed were recorded using the diary method. A research dietitian reviewed the food intakes for accuracy and classified them as A (a solid diet consisting of all foods), B (a soft diet with complete variety), and C (purees and/or liquids only).

Biochemical Measurements

Fasting blood specimens were analyzed before surgery and at 6-month intervals for blood glucose, total serum cholesterol, alkaline phosphatase, serum aspartate amino transferase (AST), serum alanine amino transferase (ALT), and serum lactic dehydrogenase (LDH).

Blood samples for vitamin determinations were drawn from the 60 patients following an overnight fast at the time body composition was determined. Serum or whole blood samples were analyzed for vitamin B-12,[12] folic acid,[13,14] and iron.[15]

Statistical Analysis

We used analysis of variance to evaluate the significance of differences. A p value of less than 0.05 was considered to be significant. Means were calculated with the corresponding standard error of the mean (SEM).[16]

Results

Body Composition, Body Mass Index, Weight

Table 1 and Figure 2 summarize the body composition and clinical results at 13.6 ± 0.4 months following operation. The patients were divided into three groups on the basis of their postoperative weight loss. Twenty-four patients had a good result, a loss of more than 25% of preoperative weight and a final weight within 30% of ideal weight. Twenty-nine patients had a satisfactory result, a loss of more than 25% of preoperative weight but a final weight greater than 30% of ideal weight. The remaining seven patients had an unsatisfactory result. Body composition data of 100 preoperative morbidly obese subjects and 25 normally nourished healthy volunteers are included for comparison. The mean preoperative body weight for each group is also included in Figure 2.

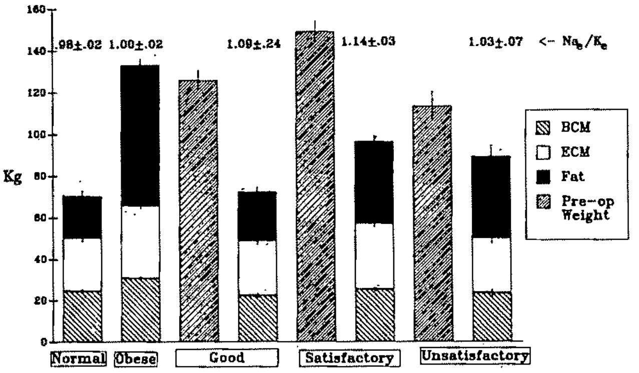
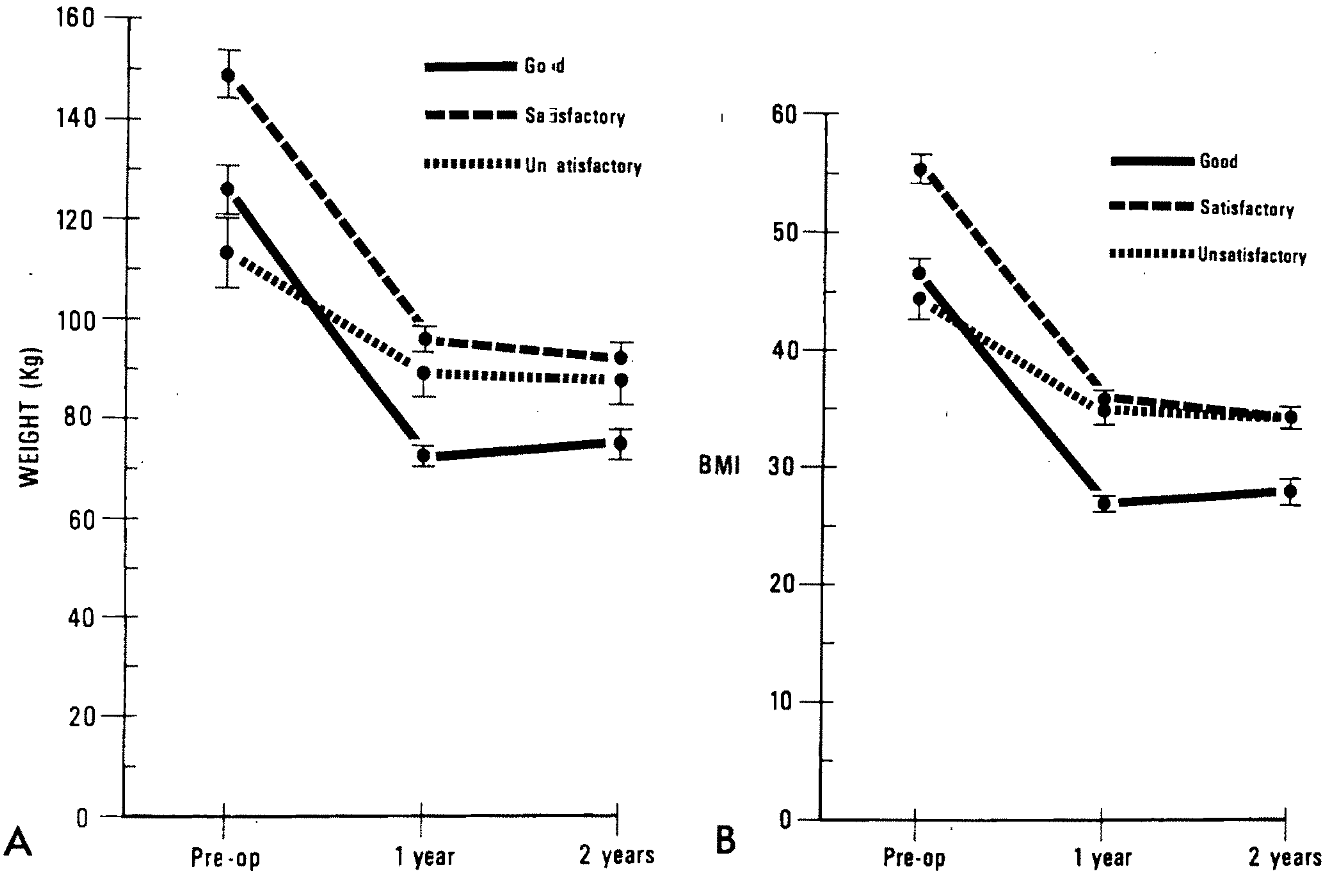


FIG. 2. Body composition of 25 normal controls (Normal); and of 100 obese patients prior to surgery (Obese); preoperative and postoperative weights and body composition at 13.6 ± 0.4 months after VBG are shown in 24 patients who achieved a good result, for 29 patients listed as satisfactory, and seven patients who achieved an unsatisfactory result. The Na_e/K_e ratio is shown for each group and controls. Malnutrition did not occur in any patient even though weight loss was rapid and great, especially in the good group. See text for definition of groups.



FIGS. 3A and B. Weight (*A*) and body mass index (*B*) changes 1 and 2 years after VBG in three groups of patients who achieved either a good, satisfactory, or unsatisfactory result. There was no significant weight change during the second year.

The mean body composition of the 24 patients with a good result at the time of evaluation was indistinguishable from normal. In spite of a mean weight loss of 41.4 ± 1.8% of preoperative weight, malnutrition did not develop. Body composition remained normal with a normal BCM and a normal Na_e/K_e ratio of 1.09 ± 0.04. The mean BMI decreased from 46.7 ± 1.2 to 27.0 ± 0.6 kg/m^2 ($p < 0.05$).

The mean weight loss in the 29 patients who achieved a satisfactory result was 34.8 ± 1.0%. However, they weighed significantly more prior to surgery than the good group ($p < 0.05$). Body composition also remained normal with a normal BCM and a normal Na_e/K_e ratio of 1.14 ± 0.03. The mean BMI decreased from 55.4 ± 1.2 to 36.0 ± 0.8 kg/m^2 ($p < 0.05$). In seven patients an unsatisfactory result occurred, with weight loss less than 25% of preoperative. Their nutritional status remained normal with a normal body composition.

The body fat of the good group returned to within normal limits. The postoperative body fat in this group was significantly ($p < 0.05$) less than the body fat in either the satisfactory or unsatisfactory groups. In all three groups no further weight loss occurred during the second postoperative year (Figs. 3A and B).

Early Surgical Follow-up

All patients with a good result and 86% of patients with a satisfactory result had an orifice of less than 11 mm in diameter at 1 year. At that time, staple line disruption had not occurred in any patient in either the good or satisfactory group.

In the unsatisfactory group a stoma size greater than 11 mm diameter was present in three patients and six of seven patients had developed a disruption in the vertical staple line.

Specific Nutritional Deficiencies

The percentage of patients with decreased serum concentrations of vitamin B-12, red blood cell folate, and serum iron are listed in Table 1. In all groups a significant number of patients had an abnormal reduction in

TABLE 2. *Diet Following Vertical Banded Gastroplasty*

Results	Total Patients	Consistency of Diet A	B	C
Good	24	9	8	7
Satisfactory	29	9	13	7
Unsatisfactory	7	3	4	0

the serum concentrations. However, a clinical deficiency state was not identified.

Dietary Habits

At 1 year 21 patients were eating a solid diet restricted only in quantity (an A result), 25 patients were ingesting a soft diet, and 14 patients were only able to take a pureed or a liquid diet. The distribution of these patients in reference to clinical result appears in Table 2. A good or satisfactory clinical result did not depend on intake of a low consistency diet. However, the majority of patients were ingesting a soft or pureed diet even a year after surgery.

Late Follow-up

All 60 patients were evaluated approximately 2 years (25.9 ± 0.8 months) after surgery, or 12.3 ± 0.8 months following the body composition measurement, to determine the stability of the weight loss (Tables 3 and 4). The method of Reinhold[11] is also included in Table 4 to evaluate weight loss as a percentage of excess weight. No patients have been lost to follow-up. Of the 24 patients with a good result at 1 year, one became satisfactory due to enlargement of the outflow banding because of migration of the polypropylene mesh into the gastric lumen. Three became unsatisfactory due to weight gain, the result of vertical staple line disruption (Table 3).

Of the 29 patients who had a satisfactory weight loss at 1 year, three patients became unsatisfactory due to disruption of the vertical staple line. However, two patients improved from satisfactory to good because of decreased caloric intake. Two patients converted from unsatisfactory to satisfactory due to slow but continued weight loss and one patient converted to good as a result of behavior modification and a decreased caloric intake. Seven patients were unsatisfactory after 1 year. After 2 years 11 had an unsatisfactory result, all due to either a staple line disruption or an outlet orifice that was too large (> 11 mm). An external band circumference that is made greater than 50 mm results in an outlet orifice as measured at endoscopy of > 11 mm.

TABLE 3. *Change in Results Between 1 and 2 Years Following Vertical Banded Gastroplasty*

13.6 ± 0.4 Months	25.9 ± 0.8 Months Good	Satisfactory	Unsatisfactory
24 Good	21	1	3
29 Satisfactory	2	23	3
7 Unsatisfactory	1	1	5
Total	24	25	11

Biochemical Results

An elevated fasting plasma glucose was present in 21 patients before surgery. The mean fasting plasma glucose was 151 ± 13 mg/dL. At the time of body composition studies the mean plasma glucose was 85 ± 3 mg/dL and was within normal limits in all but three patients. None of these patients required medication for hyperglycemia.

An elevated fasting serum cholesterol of greater than 280 mg/dL was found in only one patient. The value decreased from 286 to 237 mg/dL at 1 year. The mean cholesterol level for all patients before operation and at 1 year was 191 ± 5 mg/dL and 182 ± 5 mg/dL, respectively.

An elevated alkaline phosphatase was found before surgery in 30 patients. The mean of 142 ± 8 U/L declined to 86 ± 3 U/L at 1 year. Only four patients had a persistent elevation of serum alkaline phosphatase after operation.

Serum aspartate amino transferase was abnormally elevated before operation in eight patients to 61 ± 4

TABLE 4. *Weight Loss and Results*

	13.6 ± 0.4 Months	25.9 ± 0.8 Months
Percentage of weight loss	35.3 ± 1.3	36.1 ± 1.2
Percentage of excess weight loss	67.4 ± 2.2	66.7 ± 2.8
Result*		
Good	24 (40%)	24 (40%)
Satisfactory	29 (48%)	25 (42%)
Unsatisfactory	7 (12%)	11 (18%)
Results†		
Excellent (<25% excess weight)‡	17 (28%)	15 (25%)
Good (26–50% excess weight)	28 (47%)	27 (45%)
Fair (51–75% excess weight)	12 (20%)	16 (27%)
Poor (76–100% excess weight)	2 (3%)	2 (3%)
Failure (> −100% excess weight)	1 (2%)	0 (0%)

* See reference 4.
† See reference 11.

$$‡\ \%\ \text{excess weight} = \frac{\text{weight at evaluation} - \text{ideal weight}}{\text{ideal weight}} \times 100.$$

U/L. After surgery this returned to 18 ± 6 U/L. One patient remained abnormal after surgery. Serum alanine amino transferase was abnormally elevated before operation in 20 patients to 80 ± 12 U/L. After surgery this returned to 19 ± 3 U/L and all patients were within normal range.

Serum lactic dehydrogenase was abnormally elevated before operation in 25 patients to 279 ± 9 U/L, and in these patients it returned to 178 ± 6 U/L after operation. One patient continued to remain abnormal.

Discussion

The objective of our surgical approach to morbid obesity is to minimize the physical risks of obesity by restoring weight to within 30% of ideal without the induction of malnutrition. This was achieved in 24 of the 60 patients. At 1 year following VBG these patients had lost 41.4 ± 1.8% of their preoperative body weight. An additional 29 patients achieved a satisfactory result. In this group weight loss exceeded 25% of preoperative weight, but weight was not within 30% of ideal. At 1 year only seven patients had lost less than 25% of their preoperative weight. Their mean weight loss was 21.0 ± 0.9%.

In spite of the large weight loss at a relatively rapid rate, malnutrition did not develop in any patient. Except for excessive body fat, the body composition of all the patients at 1 year was normal with a normal BCM and a normal Na_e/K_e. The weight decrease was due to a loss of body fat without a loss of BCM. In similar studies of patients after jejunoileal bypass, horizontal gastroplasty, and gastric bypass, this degree of weight loss was associated with a significant incidence of malnutrition, which at times was life-threatening.[1,2]

The development of malnutrition following weight reduction surgery is generally not well appreciated. This is because in the studies that have monitored body composition following weight reduction surgery the LBM, not the BCM, was measured.[17,18] The LBM is not, however, a sensitive measure of the nutritional state. Malnutrition results in a loss of BCM accompanied by an expansion of the ECM and, as a result, the LBM does not change. In 75 severely malnourished individuals, there was a 41% reduction in the BCM with a concomitant 24% expansion of the ECM.[9] The LBM in these severely malnourished individuals was not significantly different from normally nourished individuals. Thus, to monitor the nutritional state following weight reducing surgery it is essential to measure the two components of the LBM: the BCM and the ECM.

We have previously reported the effect of jejunoileal bypass[2] on the nutritional status of 44 morbidly obese patients evaluated in a similar fashion. The operation involved anastomosing 15 inches of proximal jejunum, end-to-side, to 5 inches of distal ileum. Body composition remained normal after bypass in 33 patients, and at 1 year body weight had decreased by 24.4 ± 2.1%. This loss of body weight resulted entirely from a loss of body fat. Malnutrition developed in 25% or 11 patients. In these patients at 1 year the weight loss was 27.0 ± 3.0% while the BCM decreased by 22.6 ± 6.1%. Their body composition was characteristic of malnutrition with a contracted BCM, expanded ECM, and elevated Na_e/K_e. The metabolic complications associated with small bowel bypass occurred only in the patients who developed an abnormal body composition. Repeated hospital admissions were required because of these metabolic complications, which included malaise, anorexia, debilitating weakness, hypokalemia, and liver failure. Protein malnutrition was responsible for the observed abnormalities as the infusion of amino acids, without additional nonprotein calories, returned the body composition to normal and successfully corrected both the metabolic derangements and the abnormal liver function. Subsequently over several months, a high protein diet prevented the recurrence of symptoms and maintained a normal body composition. However, over several years bowel continuity was restored in almost all of the patients because of the difficulty they experienced in maintaining a high protein intake. Restoration of bowel continuity always restored both liver function and body composition to normal.

We have previously described the nutritional consequences of horizontal gastroplasty or gastric bypass[1] in 96 morbidly obese patients. In 49 patients, body composition remained normal at 24 months, with a 25.7% loss of body weight and a 36.2% loss of body fat. Malnutrition developed in 49% or 47 patients. In these patients weight loss was 25.9%, body fat decreased by 34.4%, and the BCM decreased by 29.4%. Malnutrition developed in patients with a small stoma and was associated with hair loss, lassitude, easy fatigue, and difficulty in attaining full employment. Liver failure did not occur. The body composition of all the malnourished patients eventually returned to normal. In 19 patients this occurred as the stoma enlarged spontaneously. Eight patients were successfully treated with dietary counseling. The orifice was enlarged by operation in 18 and by endoscopic dilatation in two patients.

All weight reducing operations are designed to reduce either the intake or absorption of food. To achieve adequate weight loss with jejunoileal bypass, a malabsorption state is created by limiting the length of functioning small bowel. However, if the length of small bowel remaining in circuit is too short, protein malnutrition develops. Furthermore, for the individual patient it is not possible to determine the appropriate length that must remain in circuit. The margin of error in measurement is small and hypertrophy of the remaining bowel in circuit is variable, adding to the unpredictability of this operation to produce adequate weight loss without inducing malnutrition.

The gastric weight reducing operations create a resistance to the movement of food out of the gastric pouch. With gastric bypass and horizontal gastroplasty, this is achieved by limiting both the reservoir capacity and the cross-sectional area of the outlet orifice. If the orifice is too small or eccentrically placed, vomiting and malnutrition can develop. If it is too large, weight loss is insufficient. Because the cross-sectional area is related to the $(\text{radius})^2$, small differences in the radius of the outlet orifice result in large differences in the cross-sectional area and thus to the resistance to the movement of food out of the stomach. Since narrowed orifice in the horizontal gastroplasty and gastric bypass as we performed it[1] is extremely short, it had to be constructed very small to limit flow and induce weight loss. This caused vomiting and malnutrition in a significant number of patients. This problem has been partially overcome with the VBG. With this operation, the resistance to the movement of stomach contents is not critically related to a very short but severe narrowing of the outflow tract. Vomiting is unusual after VBG for several reasons. The orifice is larger than that found effective after horizontal gastroplasty. The orifice is easily placed in the dependent position. The banding material very rarely migrates, which can cause narrowing of the orifice from the gastric pouch, and it is easier to make a smaller pouch in the vertical rather than in the horizontal position. Furthermore, by surrounding the dependent portion of the new pouch with nonelastic polypropylene mesh, the size of the orifice does not expand with time. It is not known presently how the gastric pouch changes in capacity with time. With this operation, 88% of the patients experienced a good or satisfactory result without the development of malnutrition in a single patient. This is in sharp contrast to the experience with the other weight reducing operations tested.

The operation performed in this study results in a smaller outflow tract of the new gastric pouch than the vertical banded gastroplasty described by Mason.[8] In the majority of patients the banded external circumference was 45 mm or less. The creation of an orifice of this size resulted in rapid weight loss, but was probably also responsible for the high rate of verticle staple line disruption herein reported.

At 2.2 ± 0.1 years after surgery, disruption of the staple line had developed in 14 of the 60 patients with an unsatisfactory weight loss in nine. Gastrointestinal x-ray examination and repeated endoscopy have both demonstrated that staple line disruptions enlarge with time. Most staple line perforations will probably result in an unsatisfactory result given enough time because of progressive enlargement of the communication between the new gastric pouch and the gastric fundus. This gives rise to an increased ability to eat and is associated with loss of the sense of satiety after eating small meals, which is so common in patients with intact gastric limiting operations. Loss of the feeling of satiety with small meals has prompted examination for staple line integrity in many patients and frequently has identified disruptions as the cause. Unless this complication is looked for very carefully, an inferior result can be attributed to the operation as designed.

Enlargement of the banded area of the gastroplasty occurred in only one patient in this series. This rare post-VBG complication was due to the migration of the polypropylene mesh into the lumen, with resulting enlargement of the orifice.[19] When supporting sutures, pledgets, or silicon rings are sutured to the stomach or placed near an anastomosis, migration of the material designed to maintain a constant orifice size occurs frequently.[1] All operations that depend on these materials sutured to the gastric wall or placed around or near an anastomosis are probably unacceptable. In contrast, polypropylene as used in the VBG has been dependable in maintaining orifice size with a very low incidence of migration.[19,20]

Staple line disruption occurs because the tissue between the anterior and posterior gastric walls does not heal together. In our study 4.8-mm staples were used. Lechner and Elliott[21] use 3.5-mm staples to ensure crushing and sealing between the anterior and posterior walls of the stomach. We have found that on dividing between vertical staple lines made with both 3.5- and 4.8-mm staples on the stomach, there is sufficient bleeding to require surgical hemostasis. If division between the staple lines is not done, the tissue at that site can remain viable and if the staples migrate a potential passage can develop between the new small pouch and the fundus of the stomach.

Vertical banded gastroplasty is capable of inducing impressive weight loss without malnutrition but fails in our experience, in many instances, because of staple line disruption. This complication has been previously reported.[20] For this reason we have for several months divided between the vertical staple lines in all patients undergoing VBG.

The inability to clear glucose adequately from the blood is common in obesity and may occur in the absence of clinically manifest diabetes mellitus. This was the case in 21 of the patients in this series with elevated fasting blood glucose. All but three had a complete and prompt decline in fasting blood glucose to normal with weight loss. An unsatisfactory weight loss occurred in one of the three. Several reports document the elimination of the requirement for insulin or other hypoglycemic agents in obese type II diabetics who lose weight after gastric surgery.[22,23,24]

Steatosis with abnormalities of liver function occurs commonly in obesity. In 45 of the 60 patients, one or more liver function tests were abnormally elevated before surgery. Approximately 1 year following surgery, liver function tests were normal in all but six of the 60 patients. The weight loss was good in one, satisfactory in three, and unsatisfactory in two of the six patients. In contrast, liver dysfunction is common after intestinal bypass and is especially severe in patients who develop malnutrition. Correction of the contracted BCM by intravenous amino acids or by surgical restoration of normal intestinal continuity promptly reverses even severe liver failure.[3]

All patients took a multivitamin preparation that contained 5 μg of vitamin B-12 and 0.1 mg of folic acid each day. Iron was not given routinely. No anemia developed during the 2 years of follow-up. However, serum and/or red blood cell deficiencies of vitamin B-12, folate, and iron did occur without clinical manifestation. This is in contrast to the report of Amaral et al.,[25] who described anemia in 37% of patients 20 months after gastric bypass, with a low serum iron concentration in 48.6% and a low serum vitamin B-12 concentration in 70%. These deficiency states might be expected to be lower with VBG, which does not bypass the duodenum and stomach. The final conclusion and recommendations for both operations is that careful and permanent follow-up for nutritional deficiencies be carried out.

In this study the 1983 Metropolitan height-weight tables[7] were used and the BMI[26] was calculated as (weight)/(height)^2(kg/m^2) to assess both the patients' preoperative status and the postoperative result. The BMI is a measure of the degree of obesity, with a high correlation with direct measures of body fat. It is simple to calculate and is more precise than skinfold measurements.[27]

A BMI in the range of 20–25, which was defined by Garrow[28] as Grade 0 obesity, is associated with minimal mortality and is equivalent to the insurance 'desirable weight' range. A BMI of 25–30 is Grade I obesity. The increase in mortality is minimal. Grade II obesity is a BMI of 30–40 and represents the transition from clinically trivial to crippling obesity. At the midpoint of this range, mortality is roughly double that found in the desirable weight range. Morbid obesity or Grade III obesity is a BMI over 40 and is usually incompatible with normal employment. Insurance statistics on mortality in Grade III obesity become unreliable because these individuals have difficulty obtaining insurance.[28] Patients in the upper ranges of Grade II obesity have an expected mortality three times that of individuals of normal weight in the same age group. The mortality ratio increases rapidly as BMI increases from 30 to 40.[27]

Drenick et al.[29] have reported a startling 12-fold increase in mortality in morbidly obese men between ages 25 and 34 when followed for a mean of 7.6 years. In the age group 35 to 44 years there was a six-fold excess mortality.

The effect on overall mortality resulting from a surgically induced weight loss is not easily measured at this time. While patients in the satisfactory group have lost a significant amount of weight with a decline in BMI from 55.5 ± 1.2 to 36.0 ± 0.8, it remains to be proven that this degree of weight loss will significantly decrease the physical risks associated with morbid obesity. It is likely that these patients remain at a two- to three-fold risk for mortality compared to controls of desirable weight even after surgically induced weight loss. Whether the patient has arrived at that point from a 12-fold or a four-fold increase in mortality over citizens of desirable weight is not yet clear. This type of reporting with estimates of physical risk and use of the BMI should be more widely used by surgeons assessing results in these patients.

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Immature T Lymphocytes after Injury Characterized by Morphology and Phenotypic Markers

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Changes in the peripheral blood mononuclear cell (PBMC) population in patients following both thermal and nonthermal injury were defined by both morphological characteristics and surface phenotype with the monoclonal antibodies T6, OKT9, OKT10, and OKIa1, using a fluorescence activated flow cytometer with gating to separate small cells of the lymphocyte series from larger forms. Lymphocytes with surface antigens that bind T6, OKT9, and OKT10 are rarely found in the peripheral blood of adult patients, except in those with malignancies of the lymphoid system. In both burn and trauma patients the percentage of lymphocytes in the PBMC population after Ficoll-Hypaque separation was significantly reduced as compared with normal controls due to increases in the number of granulocytes, large granular lymphocytes (LGL), and monocytes, often present in immature forms. T6 cells were found in significantly greater numbers in both burn and nonthermal injury patients than in a control group using both small and wide gate settings on the fluorescence-activated flow cytometer. Significant increases in the number of $T9^+$ cells also were observed in both groups for a prolonged period following injury. Significantly increased numbers of the $T10^+$ and $Ia1^-$ cells were detected in burn patients. The response to injury, therefore, involves the appearance in the peripheral blood of immature cells that may express T6, T9, T10, and Ia1 surface antigens. These cells may be present in quantities otherwise seen only in malignant disease.

PATIENTS WHO SURVIVE the initial shock phase after major injury have an increased susceptibility to overwhelming sepsis that is frequently fatal.[1] This has been attributed to abnormalities of cell-mediated immunity. In burn patients, *in vivo* anergic responses to skin test antigens, decreased *in vitro* blastogenesis in response to T cell mitogens, reduced IL 2 production by lymphocytes, and suppressor cell activity in mixed lymphocyte culture have all been described.[2–4] Similar but less frequent findings have also been reported after major nonthermal injury.[5,6] Characterization of peripheral blood mononuclear cells (PBMC) obtained from patients after all types of trauma is therefore of considerable interest.

The development of an extensive repertoire of monoclonal antibodies (McA) that recognize antigens expressed on T cells both during development and in maturity has allowed the documentation of alterations in T cell subsets in disease states, and the delineation of thymocyte development. Using the OKT series, 70% of the total thymic cell population are $T4^+$, $T8^+$, $T6^+$, and $T10^+$, but on full maturation and export from the thymus T6 and T10 expressions are both lost.[7] As a result, PBMCs contain less than 1% $T6^+$ cells and very limited numbers of $T10^+$ cells.[7–9] The T9 antibody, which binds to both immature thymocytes and activated mature T cells, has been shown to recognize the transferrin receptor on these cells,[10,11] but normally less than 9% of PBMC are T9 positive.[8] OKIa1 also binds to activated T cells, B cells, and monocytes. In a variety of malignancies of the lymphoid system, circulating neoplastic cells that react with T6, T9, and T10 can occur in considerable numbers,[7,8,12] but otherwise cells of these phenotypes are rarely seen in the PBMC of adults.

In this study we have identified on morphologic grounds increased numbers of immature leukocytes in the cell population obtained after Ficoll-Hypaque separation of peripheral blood from both thermal and nonthermal injury patients. Examination of their T cell antigens revealed significantly increased numbers of cir-

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culating T6, T9, and T10 positive cells among the burn patients' PBMCs, and increased numbers of T6 and T9 cells from trauma patients. This response to injury has not been previously reported, and its significance is discussed.

Methods

Subjects Studied

Three groups of subjects were studied. Thirteen burn patients (3 women, 10 men) aged 23–91 years (mean: 53.4) admitted to The Longwood Area Trauma Center at the Brigham & Women's Hospital with burns from 5 to 80% total body surface area (mean: 34%) comprised the first group. The second group consisted of nine patients (2 women, 7men) aged 16–42 years (mean: 22.4), who suffered a variety of moderate to severe nonthermal injuries, often multiple, ranged as assessed by the Injury Severity Score[13] from 9 to 40 (mean: 21.8). Both groups were studied weekly until discharge from the unit or death. Informed consent was obtained and the study approved by the Human Subjects Committee of the Brigham & Women's Hospital. These two groups were compared to a third group of 16 healthy volunteers (9 women, 7 men) aged 18 to 35 years (mean: 27.6), who comprised the controls.

The patients received conventional intensive care, including elective intubation for lung injuries, vigorous fluid replacement with close monitoring, and early excision and grafting or full thickness and deep partial thickness burns. Particular attention was paid to nutritional status and requirements. All patients were assessed shortly after admission and, if necessary, provided with full nutritional support by the intravenous route. Caloric requirements and nitrogen balance were continuously assessed and intake adjusted daily where needed.

Preparation of PBMCs

Peripheral blood was collected between 7:30 and 9:30 A.M. into heparinized 50 cc syringes. It was diluted 1:2 in phosphate-buffered saline (PBS), then placed over one-third this volume of Ficoll-Hypaque (Pharmacia, Piscataway, NJ) and centrifuged for 35 minutes at 400 g. The interface cells were collected, washed three times in minimal essential medium (MEM) (Eagle), and counted using trypan blue for assessment of viability, which was always more than 95%. The number of true mononuclear cells was estimated on a hemocytometer using a sample specimen in Turk's stain, other cell types being excluded from the count on morphological grounds. The mononuclear cells were then suspended at 5×10^6/ml in MEM with 2 mM-glutamine, 5% fetal calf serum (FCS, MA Bioproducts, Walkersville, MD), and 1% antibiotic/antimycotic solution containing 10,000 units penicillin/10,000 μg streptomycin/20 μg Fungizone per ml (Grand Island Biol. Co., NY).

Morphologic Assessment of PBMCs

PBMCs were diluted to 2×10^6/ml in MEM and an equal volume of 30% human albumin added. Two hundred microtiters of this suspension was centrifuged onto a slide using a Shandon-Cytospin (Shandon Southern Instruments, Inc., Sewickly, PA) at 900 rpm for 7 minutes, then stained with Wright-Giemsa. All the slides were examined by the same observer (MLR) using light microscopy at 1000× and classified by conventional hematological criteria into the following categories—granulocytes (PMN, bands, and less mature granulocytes), lymphocytes, atypical lymphocytes (including blasts), monocytes, and large granular lymphocytes (LGL). The observer was blind as to the origin of the cells being studied. High power fields were examined and the number of each cell type expressed as a percentage of the total counted.

Staining with Monoclonal Antibodies

An indirect technique was employed modified from the procedure recommended by the manufacturers of OKT3, OKT4, OKT8, OKT9, OKT10, and OKIa1 (Ortho Diagnostic Systems, Raritan, NJ). The T6 McA was a generous gift from Dr. Cox Terhorst of the Dana-Farber Cancer Institute, Boston, MA, and has been used extensively.[14] McA OKT3 recognizes cluster designation (CD) CD3, OKT4, CD4, and T6, CD1. Overnight incubation at 4 C of 100 μL of PBMC at 5×10^6/mL with 5 μL of McA produced good binding of McA to cell, and has been used throughout our work. Cells were then washed in PBS, and 100 μL of fluoresceinated goat anti-mouse Ig (Tago, Burlingame, CA) diluted 1:30 in MEM then added. After 45 minutes incubation at 4 C, the cells were washed twice in PBS and diluted with 1 cc of 1% paraformaldehyde in PBS and stored at 4 C prior to counting. Negative control cells were stained with fluoresceinated anti-mouse Ig (FITC) only. At least one control was assayed one each occasion patients were studied.

Modification of the monoclonal staining procedure made the timing more convenient and improved staining. This modification included overnight, rather than 2 hour, incubation of cells with the monoclonal antibody, followed the next day by washing and staining with the fluoresceinated anti-mouse Ig. Since this procedure differs from that currently recommended by the manufacturers of the monoclonal antibodies (Ortho Pharmaceuticals), experiments were done to compare overnight with the recommended 2-hour incubation period. In these experiments, nine normal controls were studied in nine different observations, and two thermal injury patients were studied for six observations. The results showed no significant differences with any monoclonal antibody tested, including OKT3, OKT4, T6, OKT8, OKT9, OKT10, and OKIa1 when compared by the Wilcoxon matched pairs analysis ($p = > 0.05$).[15] Early experiments done during this study with the assistance of Dr. Stuart Schlossman's laboratory (Dana Farber Cancer Institute, Boston, MA) had shown that there was no difference between background staining without the use of an irrelevant monoclonal mouse IgG, or with its use followed by fluorescent staining. However, these early experiments were only done with the three monoclonal antibodies OKT3, OKT4, and OKT8. We therefore carried out similar experiments with the remaining monoclonal antibodies used in this study (T6, OKT8, OKT9, OKT10, and Ia), and found no difference ($p = >0.05$) when cells were stained either with FITC alone or with irrelevant monoclonal Ig (MOPC-21, Litton Bionetics, Kensington, MD). No significant difference was observed between staining for either 2 hours or 24 hours with or without MOPC-21 as the control antibody ($p = >0.05$).

Flow Cytometry

Positive staining of PBMC by McA was determined by forward light scatter on a Becton-Dickinson Flow Cytometer (Becton-Dickinson, Mountain View, CA). Over 90% of the measurements were made by the same observer. After calibration of the cytometer with latex beads, a sample of OKT3-labelled cells from a control subject was used to adjust the cytometer gate to the size of normal mature T cells and measurement of control and patient OKT3 (CD3), OKT4 (CD4), and OKT8 (CD8) cells was performed. Assessment of positively staining cells of various sizes was important because we had observed that the patients' PBMC populations contained LGL, atypical lymphocytes, PMN, and blasts that had been shown on occasion to bind various McAs. Altering the gates permitted the exclusion of most of these cells, counting only those corresponding in size to the normal T cell population. This is of particular importance when mature cells are to be measured. As the T6, T9, and T10 markers can be found on immature cells that are morphologically larger than mature cells, two measurements were usually made—for "small" gates (*i.e.*, cells the size of control T3 cells) and for "wide" gates (this included any larger cells that might be present). The number of positive staining cells passing through each gate after subtraction of background staining was expressed as a percentage of total number of cells counted.

Statistical Analysis

Examination of the data suggested that its distribution was nonparametric, and this was confirmed using a normal probability plot. Some values are reported as means ± standard error of the mean (SEM) according to convention, but in order to depict more accurately the data, dot plots are presented. Statistical comparisons used the Mann-Whitney U Test and the level of significance was taken at $p = <0.05$. When comparison of staining methods were analyzed for significance, the Wilcoxon matched pairs analysis was used.

Results

Cellular Morphology of PBMC from Burn Patients (Table 1)

When smears of the PBMC populations were examined, obvious abnormalities were seen. Particularly striking was an increase in the number of cells showing features of immaturity (*e.g.*, banded nuclei, granular cytoplasm, and occasionally mitotic and multinucleate cells). Identification of such cells as being of a particular cell-type may be difficult, but when classified into the categories described above and compared to controls significant differences emerged. The controls showed that our technique of Ficoll-Hypaque separation was normally effective in removing almost all granulocytes and yielded a mean of 95% mononuclear cells. The main differences seen in the patients were an increase in granulocytes in particular, and sometimes also in monocytes, these occasionally occupying over 60% of the population. As a result, the percentage contribution of lymphocytes was reduced and a significant late increase in LGL was observed. Atypical lymphocytes were seen more frequently, but this apparent increase was never statistically significant at any time period.

Cellular Morphology of PBMC from Trauma Patients

Examination of the morphology of PBMC from patients after nonthermal injury revealed changes similar to those following burns. Overall there was a significant reduction in the number of lymphocytes (mean: 58.6%, SEM: 4.0, median: 62.5%, $p = 0.0002$), and a significant increase in the number of LGL (mean: 5.7%, SEM: 1.14, median: 4.0%, $p = 0.0006$). The number of lymphocytes was reduced for the periods 0–9, 10–19, and 20–29 days and then recovered. The number of monocytes was increased during days 10–19 (mean: 31.6%, SEM: 5.8, median: 27%, $p = 0.002$), whereas the increase in LGL was during the periods 20–29 and 30 days onward.

TABLE 1. *Morphology of "Mononuclear" Cells Isolated by F/H Gradient in Burn Patients and Controls**

	Control†	Burn Patient Days After Injury			
		0–9 Days	10–19 Days	20–29 Days	30 Days†
Granulocytes					
Mean	3.57%	17.75%	31.2%	8.4%	10.9%
SEM	0.75	5.85	9.47	3.9	1.9
		NS‡	p = 0.02	NS	p = 0.0005
Lymphocytes					
Mean	85.1%	56.2%	51.33%	49.9%	63.2%
SEM	1.9	8.4	11.5	9.4	7.2
		p = 0.009	p = 0.02	p = 0.02	p = 0.001
Atypical lymphocytes					
Mean	2.14%	3.91%	2.67%	4.25%	4.2%
SEM	0.63	1.7	1.6	1.9	1.2
		NS	NS	NS	NS
Monocytes					
Mean	8.14%	21.7%	10.9%	28.4%	10.1%
SEM	1.76	7.9	2.89	8.5	3.28
		NS	NS	p = 0.03	NS
Large granular lymphocytes					
Mean	1.14%	1.56%	2.9%	9.83%	9.7%
SEM	0.56	0.57	0.77	4.3	6.0
		NS	NS	p = 0.007	p = 0.05

* The number of cells of each type expressed as a percentage of the total number of cells counted.

† Results from 14 different normal controls. Burn patients, 12 patients followed after injury during indicated days.

‡ NS = $p > 0.05$ by Mann Whitney Test.

Burn Patients—T6 Positive Cells (Fig. 1)

Using small gates, 21 measurements were made of the controls and failed to detect circulating $T6^+$ cells on 12 occasions. The mean value was 1.85% (SEM: 0.96) and median was 0. When larger cells were included using wide gates, more $T6^+$ cells were detected (mean: 3.08%, SEM: 1.03, median: 2.0%).

Burn patients were often found to have increased numbers of circulating $T6^+$ cells, and sometimes a sizeable population of these cells was present. When the total number of measurements on patients were compared to the controls a significant increase was observed. (Patients mean % $T6^+$ cells with small gates: 6.54%, SEM: 1.51, median: 4.0%—patients *vs.* controls, $p = 0.0081$). (Using wide gates, patients T6 positive cells —mean: 11.5%, SEM: 2.2, median: 9.0%—patients *vs.* controls, $p = 0.015$). For analysis of changes with time following injury, successive 10-day periods were considered, and each compared to controls. Significant increases in $T6^+$ cells ($p < 0.05$) occurred at days 0–10 and day 41 onward measuring small cells and using wide gates from 0 to 10 days, and from 11 to 30 days when two periods were combined.

Burn Patients—T9 Positive Cells (Fig. 2)

In 34 measurements of control PBMC using small gates, circulating $T9^+$ cells were absent or undetectable on 16 occasions. Overall the mean number of these cells was 1.82% (SEM: 0.47) and the median was 0. The corresponding values using wide gates were mean: 4.66, SEM: 1.28, and median: 3.5%.

The data analyzing small cells from burn patients re-

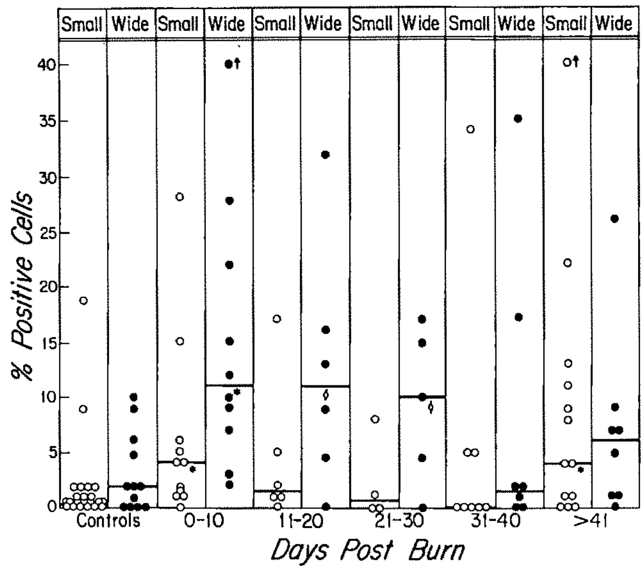

FIG. 1. *T6 positive cells following thermal injury.* Individual data points are shown using the small gate (O) and wide gate (●) setting on the FACS (see text), with the median value for each period indicated by the horizontal bar. More than 40% indicated by †. (*$p < 0.05$, patients *vs.* controls, and §$p < 0.05$ when the period 11–30 days considered.)

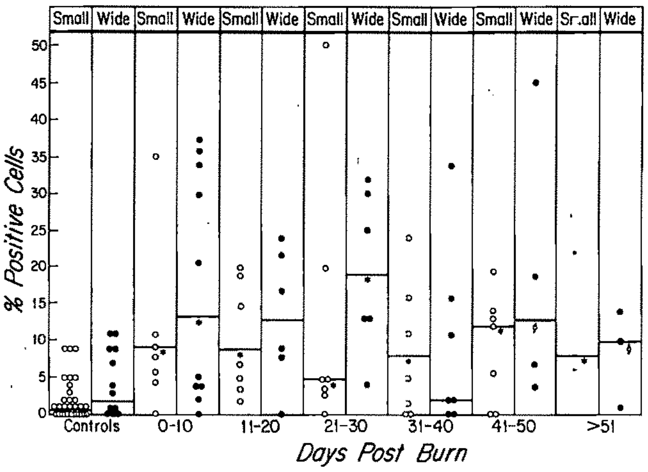

FIG. 2. *T9 positive cells following thermal injury.* Individual data points are shown for the small (○) and wide gate (●) setting on the FACS and the median value for each period indicated by the horizontal bar. (*p < 0.05, patients *vs.* controls, §p < 0.05, 41 days plus, patients *vs.* controls.)

vealed a consistent and statistically significant ($p < 0.05$) increase in the number of $T9^+$ PBMC throughout the study, in each 10-day period. In contrast to the controls, circulating $T9^+$ cells were undetectable in patients in only six occasions out of 42 measurements. Overall using wide gates, a significant increase in $T9^+$ cells was seen (median: 12.0%, $p = 0.007$). At all periods but one (31-40) there were increased numbers of T9 cells and this reached significance ($p < 0.05$) on days 0-10, 21-30, and when the periods 41-50 days and 51 plus days were combined).

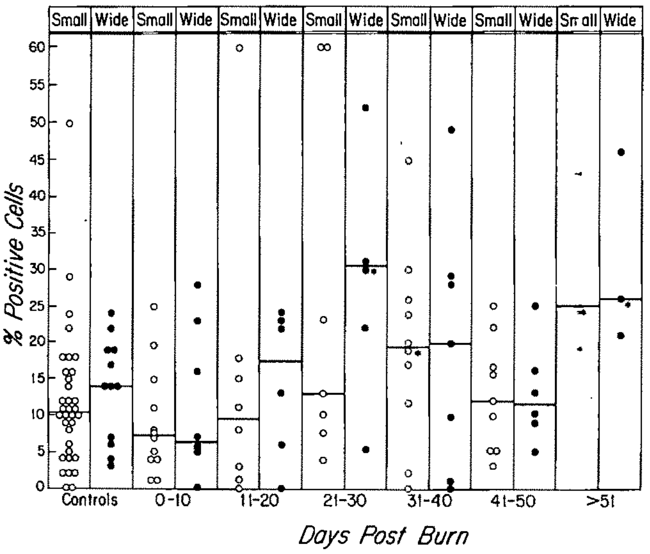

FIG. 3. *T10 positive cells following thermal injury.* Individual data points are shown for small (○) and wide gates (●) on the FACS and the median value for each period indicated by the horizontal bar. (*p < 0.05, patients *vs.* controls.)

Burn Patients—T10 Positive Cells (Fig. 3)

Thirty-four measurements of controls using small gates revealed a mean value of 11.8% (SEM: 9.6) and median of 10.5%. The patients overall had a slight increase in the number of $T10^+$ cells (mean: 17.3%, SEM: 2.5, median: 12.5%), but this failed to reach statistical significance ($p = 0.2$). When studied over time, however, significant increases were observed at 21-30 days and 51 plus days after injury ($p = 0.04$ and 0.015, respectively). On occasions it was possible to detect a population of $T10^+$ cells present in considerable numbers.

When the flow cytometer was set to use wide gates, the values obtained for controls were mean: 13.5%, SEM: 1.89, and median: 14%, and for the total burn group 18.3%, SEM: 2.3, and median: 18%. This difference was not significant ($p = 0.29$); however, significant increases were observed at 21-30 days following injury (median: 30.5, $p = 0.03$) and 51 plus days (median: 26, $p = 0.02$).

Burn Patients—Ia1 Positive Cells

Using small gates the mean per cent Ia1 positive cells in controls was 9.6%, SEM: 1.1, median: 8.75%. During the period 41 days onward, the number of $OKIa1^+$ cells was increased in burn patients (mean: 21.5, SEM: 4.7, median: 20.0, $p = 0.035$), but although increased at other times this failed to achieve statistical significance ($p > 0.05$).

When the gates were increased to include larger cells, however, an overall increase in $Ia1^+$ cells was observed (Controls' mean: 15.08%, SEM: 2.16, median: 15.0%; Patients' mean: 24.0%, SEM: 2.4, median: 22%; $p = 0.017$). Increased numbers of $OKIa1^+$ cells were observed during the 21-30 day period (mean: 40.6%, median: 35.3%, $p = 0.009$), during 31-40 days (mean: 22.7%, median: 23%, $p = 0.055$), and from 41 days onward (mean: 23.6%, median: 22%, $p = 0.04$).

Trauma Patients (Fig. 4)

Circulating $T6^+$ cells in the trauma patients were identified on 16 occasions out of 24 measurements using small gates, contrasting with only nine out of 21 measurements in the controls. Similarly using wide gates, we were only unable to detect T6 cells on two occasions from 15 patient assays. When all the data obtained using small gates were compared, a significant increase in the number of circulating $T6^+$ cells was noted (controls' mean: 1.86%, SEM: 0.96, median: 0; trauma patients' mean: 7.2%, SEM: 2.3, median: 3.0%, $p = 0.04$). Similarly, when the wide gate setting was employed an increased number of $T6^+$ cells was observed (controls' mean: 3.08%, SEM: 1.03, median: 2.0%; patients' mean: 15.1%, SEM: 4.6, median: 9.0% $p = 0.04$).

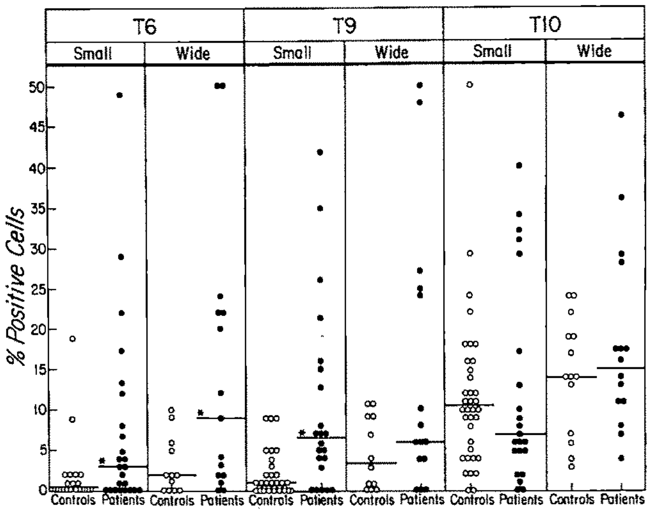

FIG. 4. T6, T9, and T10 positive cells after nonthermal injury. Individual data points are shown for controls (O) and patients (●) and the median values indicated by the horizontal bar. (*$p < 0.05$, patients *vs.* controls.)

When the data for T9$^+$ cells were examined, significantly increased numbers were detected using the small gates (controls' mean: 1.82%, median: 0; patients' mean: 10.2%, median: 6.5%, $p = 0.0017$). Using the wide gate setting the maximum number detected in the controls was 11%, and this was exceeded on five occasions in the patients—a significant difference using chi squared analysis ($\chi^2 = 4.91$, $p < 0.05$ for 1 df). The increase in the median from 3.5% to 6.0% for the group, however, failed to reach significance ($p = 0.2$).

Although on five occasions the patients had over 25% circulating T10 positive cells measured using small gates, the group had a slightly lower median value than the controls. Using the wide gate setting a population of T10 positive cells was also detected on a few occasions, but no significant difference between the controls and the trauma patients could be established.

There were insufficient data on trauma patients to permit a study over time following the injury, and in general this rather heterogenous group of patients were in hospital for less time than the burn patients. No clear picture of changes following injury emerged for T6$^+$ and T10$^+$ cells, although like the burn patients the increase in small T9$^+$ cells was probably present throughout the study period.

Discussion

The data presented here demonstrate that following injury the cellular composition of the PBMC population changes markedly with an increase in cells bearing T cell markers not normally found in peripheral blood. Examination of the morphology of the cells obtained after Ficoll/Hypaque separation revealed increased numbers of granulocytes, monocytes, LGL, and fewer mature lymphocytes. Immature lymphoid and myeloid cells were present in significant numbers as well as nucleated red cells and occasional mitotic figures. This has been described in burn patients by Volenec and colleagues[16] and a detailed study of this phenomenon in a larger group of patients has been submitted for publication.[17] The finding of similar changes after nonthermal injury suggests that this is part of the response to all types of injury. The presence of these cells suggested that cells of immature phenotype may also be present and prompted this investigation. Populations of cells positive for T6 (CD1), T9, T10, and Ia1 were identified frequently in burn patients, and nonthermal injury patients had significantly increased numbers of T6 and T9 positive cells.

The techniques of McA labeling and measurement of positively stained cells described here are based on those recommended by the relevant manufacturers and used standard reagents and equipment used widely elsewhere. However, certain departures from recommended and established protocols, and possible limitations of our techniques need to be discussed. As stated, our data (see Methods) showed that background staining using anti Ig-FITC alone or an irrelevant mouse McA and anti-Ig FITC gave similar results, so we adopted the former technique. However, where it appears that abnormal cell populations are present, some of which may contain a large number of Fc receptors,[16] the two methods could yield slightly different results, and this may account for a small part of the differences observed between controls and patients. It seems highly unlikely, however, that this explains the existence of large populations of cells quite separate from the background area, which we have frequently seen, that are described here. Although there are advantages to using flow cytometry to measure positively stained cells, such as heterogeneous cell population makes it impossible often to define the T cell constituent when using foward light scatter.

In normal PBMC suspensions it is possible to distinguish fluorescence due to the erythrocytes and due to PMNs and other larger cells, and a well defined T3$^+$ population often exists in between these. Because this was not the case when we began to study trauma and burn patients, it was recommended by Dr. Kenneth Ault, of the Brigham & Women's Hospital Analytical Cytology Laboratory, that we use a control T3 stained specimen to define the T cell population by size and to use this setting of the gates (called small gates to determine changes in the T cell subsets in patients. The wide gates setting (which included all the larger cells) was also used to provide, by comparison, information about the phenotypes of the larger cells within the PBMC population. It is important to state that the numbers obtained and reported here represent the percentage of cells passing through the gate that stain positively with the McA used, and cannot be extrapolated back to the peripheral blood to give absolute numbers of each circulating cell type for each patient. It has been suggested that this technique gives more consistent results from day to day[18] and indeed our range for the commonly used T3, T4, and T8 markers are very similar to those described by others.

With these reservations, we feel that these data show clearly that after thermal injury T6$^+$, T9$^+$, and T10$^+$ cells can be found in the peripheral blood, and T6$^+$ and T9$^+$ cells after nonthermal injury. What are these cells? When Wright-Giemsa stained smears of PBMC were examined, we found increased numbers of immature lymphoid cells, and also identified in both patient groups frequent increases in the contribution of LGL, granulocytes, and monocytes to the PBMC pool. Ortaldo et al.,[19] having obtained purified suspensions of these cell types by a variety of techniques, examined the percentage of cells that would bind a number of T cell McA. Less than 1% of PMN were T6$^+$, T10$^+$, or Ia$^+$, and only 1% of LGL, T6 positive. On average 35% of LGL were Ia$^+$ and 62% T10$^+$, leading to the suggestion that OKT10 was a useful marker for LGL. Monocytes showed widespread nonspecific low affinity binding, but specific binding only for OKM1 and Ia. This suggests that the T6 cells we identified are unlikely to be PMN, LGL, or monocytes. However, it is quite possible that the T10$^+$ cells occasionally seen are LGL.

A more likely explanation is that these McAs identify immature T cells, and that extrathymic maturation of T cells occurs in burn and trauma patients. This is supported by the morphological appearance of the PBMC where immature forms were frequently seen, and by the fact that the T6, T9, and T10 antigens are associated with various stages of intrathymic maturation. In addition, cord blood from normal full-term infants has been shown to contain on average 24% T6 positive cells and 58% T10 positive.[20] It is now realized however that these markers are not specific for thymocytes. Bone marrow cells have been examined for T cell markers and about a third of all cells were found to be T10 positive.[21] Immature B cells were very frequently OKT10$^+$, whereas mature B cells and erythroid precursors were T10 negative. No T6$^+$ cells were identified in bone marrow, but T6$^+$ cells have been identified in the tonsil and in lymph nodes.[22] Of particular importance is that the T6 McA will identify the Langerhans cell of the epidermis.[23] These cells are the principal antigen presenting cells in the skin and, as much, initiate the response to foreign antigen.[24] Although originally thought to be fixed, it is now clear that the Langerhans cells or their precursors circulate between the skin and local lymph nodes and, if depleted, are repopulated from the bone marrow.[25] A full-thickness burn will by definition destroy these cells and the larger T6$^+$ cells identified in the PBMC population may be circulating Langerhans cells or precursors engaged in repopulation of the regenerating or grafted skin.

Several studies have shown that activation of T cells produces changes in the surface antigens with the appearance of markers normally associated with immaturity. Hercend et al.[26] showed that activation of T cells by PHA, soluble antigen, or in mixed lymphocyte culture produced, as proliferation occurred, cells that were T9$^+$, T10$^+$, and IaI$^+$. This was confirmed by Burns et al.,[27] who also showed that T cells increase in size on activation but do not become T6 positive. It is now known that OKT9 recognizes the transferrin receptor present on dividing cells, including myelocytes and nucleated erythroid precursors from bone marrow, and immature thymocytes.[10,11] Aside from the increase in immature cell types found in turn and trauma patients, including nuleated red cells, evidence suggests that their PBMC population contains activated cells. Sakai, Daniels, and colleagues found that unstimulated PBMC showed considerable spontaneous activity in tissue culture as assessed by the incorporation of radiolabelled nucleic acid precursors,[28] and we have confirmed these findings in our laboratory. The consistent increase in small T9$^+$ cells seen here probably represents activated T cells. Circulating T10$^+$ cells were seen more frequently in burn than in trauma patients, but we are unable to explain this difference.

What are the implications of these findings? They suggest that following injury, just as immature PMN are released into the circulation, so is a population of immature T cells presumably destined to replace those that may be lost through hemorrhage or destruction at the injury site. That extrathymic development of T cells occurs is demonstrated by studies on athymic mice and man. Athymic mice still develop T cells and interestingly T6$^+$, T9$^+$, and T10$^+$ PBMCs were found in studies of patients with the DiGeorge Syndrome, a condition of congenital thymic aplasia.[29] Other than this rare condition, significant numbers of T6$^+$ and T9$^+$ cells are only detected in various types of T cell neoplasias and in cord blood.[20] This immaturity of the T cell population probably contributes to the decreased T cell response observed in these patients by many investigators.

These findings have important implications for work in this field. First, it is clear that the cells recovered after Ficoll-Hypaque separation of peripheral blood contain not only a considerable number of cells not of the lymphocyte series, but those T lymphocytes present frequently display markers of immaturity. If this "contamination" by PMNs and blasts is not accounted for in the dilutions necessary to prepare the final PBMC suspension, then spuriously low results from *in vitro* assays of lymphocyte function may be obtained. In addition, these data raise the question as to whether the principal immunological abnormality in burn and trauma patients is merely the functional immaturity of the circulating lymphocyte pool. Certainly Volenec and colleagues[16] found that burn patients with persistent immature cells within the PBMC had a worse prognosis than those with only transient abnormalities. However, it would be difficult to explain the presence of serum suppressive of lymphocyte function[2] and suppressor cells on this basis. Immature lymphocytes within the PBMC population may contribute to the abnormalities of lymphocyte function observed and are a potential target for immunomodulation.

In conclusion, following injury large populations of T6, T9, and T10 positive cells appear in the circulation. These cells can be identified within the PBMCs after Ficoll/Hypaque separation. Morphologic examination of these cells shows the presence of immature lymphoid and myeloid forms and suggests that this unusual T cell profile represents the appearance of immature T cells in the peripheral blood.

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Carcinoma of the Ampulla of Vater

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Thirty-five consecutive cases of adenocarcinoma of the ampulla of Vater seen over the past 36 years were reviewed The introduction of new diagnostic techniques over the course of this study improved the accuracy of preoperative diagnosis but did not lead to earlier diagnosis. The surgical resectability rate was 88%, and 53% of postoperative survivors were free of disease at 5 years. Of the 14 patients with metastases to regional lymph nodes, 27% survived disease-free for 5 years. Surgical mortality was 25% for the entire series but has been reduced to 6.6% over the past decade. Surgical mortality was primarily due to leakage of the pancreaticojejunostomy; the risk of pancreaticojejunostomy leak correlated inversely with the degree of chronic pancreatitis in the pancreatic remnant. In 35% of resected cases, a benign adenomatous component was contained within the cancer of the ampulla of Vater. Cure rates are good for this lesion. The most important factor in maximizing cure rate is careful attention to the technical details of pancreaticojejunostomy in order to minimize surgical mortality. Benign adenomas appear to be a frequent precursor of carcinoma of the ampulla of Vater.

THE PERIAMPULLARY AREA is anatomically complex and adenocarcinoma may arise from one of four types of epithelium: the mucosa of the ampulla of Vater, the pancreatic duct, the distal common bile duct, or the periampullary duodenum. Carcinomas from each of these four sites of origin may exhibit different growth patterns and different natural histories. In the clinical situation, the site of origin cannot always be distinguished, and surgical treatment for all resectable carcinomas in the periampullary area is essentially the same. However, when reviewing the natural history, cure rates, and nuances of diagnosis and surgical care, it is advantageous to separate these four lesions as clearly as possible.

Carcinoma of the ampulla of Vater is considered together with other periampullary cancers in most reports.$^{1-4}$ Furthermore, the criteria by which a cancer is judged to be ampullary in origin has not always been clear in previous reports.$^{2-6}$ In our experience, histology is not always helpful in distinguishing among the various sites of origin; this distinction is best made on the basis of gross surgical anatomy. The natural history may be obscured by inclusion of large tumors that encompass the distal bile duct and ampulla and invade the periampullary pancreas and duodenal wall such that an ampullary origin cannot be assigned with confidence. Conversely, overly rigid criteria may cause all but the smallest and most favorable lesions to be excluded.

To clarify the presentation, natural history, surgical resectability, cure rate, and distinctive features of diagnostic work-up and surgical technique, we revived our experience with carcinoma of the ampulla of Vater.

Materials and Methods

Hospital files and pathology records were systematically searched and records were identified and reviewed of all patients classified as having neoplasms of the periampullary region, head of the pancreas, ampulla of Vater, distal bile duct, or duodenum. From this group, patients with neoplasms of the ampulla of Vater were selected, using the preoperative diagnostic evaluation, surgeon's note, gross pathologic description, histology, and often specimen photographs (Figs. 1 and 2). In most cases, the gross surgical pathology and specimen photographs were most helpful. Cases in which the mucosa of the ampulla of Vater could be clearly identified as the site of origin of the tumor (*i.e.*, tumor confined to the ampulla of Vater or clearly infiltrating out from it into

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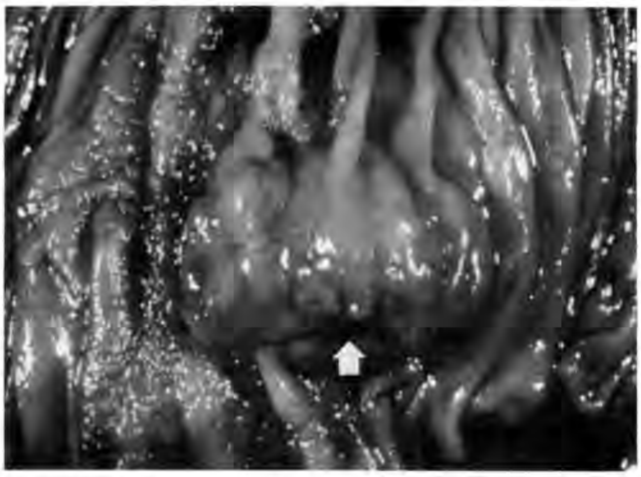


FIG. 1. Gross specimen of carcinoma of ampulla of Vater. The ampullary orifice is at the interior aspect of the tumor mass (arrow).

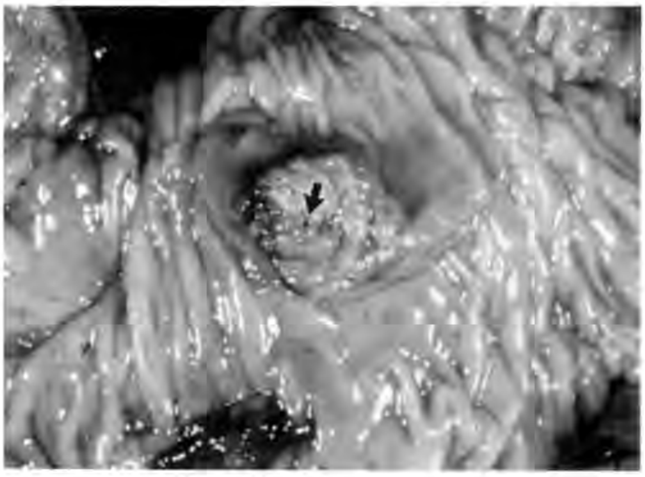


FIG. 2. Gross specimen of carcinoma of ampulla of Vater. The ampullary orifice can be seen in the center of the tumor mass (arrow).

the periampullary tissues) were included. Doubtful cases, where the site of origin could not be clearly assigned, were uncommon but were excluded from this series.

The cases were then submitted to intensive clinical and histopathologic review analyzing features of presentation, demographics, details of preoperative work-up, surgical treatment, postoperative follow-up, and histopathologic features. Survival rates were calculated by the product limit method of Kaplan and Meier.[7] Statistical comparisons were made using χ^2 analysis.

Results

Of 37 cases identified as neoplasms of the ampulla of Vater during the period of study (1949–1985), two were benign villous adenomas. The age of the 35 patients with malignant lesions ranged from 41 to 83 years with a median age of 62 years. Twenty-six patients were men and 11 women. The most common presenting signs are summarized in Table 1. The classic triad of fluctuating painless jaundice, palpable gallbladder, and anemia was present in only two patients. In nine patients, cholecystectomy had been performed within 10 months of diagnosis of carcinoma of the ampulla of Vater in the erroneous belief that the patients had only biliary stone disease.

Preoperative evaluation became much more accurate over the course of this study, largely due to the introduction of fiberoptic upper GI endoscopy and endoscopic retrograde cholangiopancreatography. An accurate preoperative diagnosis of carcinoma of the ampulla of Vater was established in 27% of patients prior to 1969, whereas after 1969 the preoperative diagnosis was correctly established in 73% of patients. However, the introduction of better diagnostic techniques did not improve the stage at diagnosis as judged by the status of the regional lymph nodes in resected specimens. Six of 17 patients prior to 1969 had positive nodes in their resected specimens, while eight of 14 patients after 1969 had positive nodes.

In 31 of 35 patients (88%) with malignant lesions, radical resections could be carried out (30 Whipple resections, 1 total pancreatectomy). In the remaining four patients, metastatic disease at presentation precluded radical resection and bypass alone was performed. One of two patients with benign villous adenomas underwent Whipple resection and the other underwent local resection. Of the 32 patients undergoing radical resection (31 for carcinoma, 1 for villous adenoma), there were eight postoperative deaths (25%). Postoperative mortality declined steadily throughout the period of study (Table 2) and over the past decade has been 6.6 ($p < 0.05$, comparing the last 10 years of study with the previous years of study). The causes of the surgical mortality are listed in Table 3. By far the most common cause of perioperative mortality was intra-abdominal sepsis due to leakage of the pancreaticojejunostomy. Of nine confirmed pancreaticojejunostomy leaks, six proved fatal.

TABLE 1. *Presenting Symptoms and Signs of Ampullary Carcinoma*

	(%)
Jaundice	81
Weight loss	70
Abdominal pain	62
Occult blood in stool	45
Anemia	38
Anorexia	35
Pancreatitis	5

TABLE 2. *Surgical Mortality by Decade: Radical Pancreaticoduodenectomy for Carcinoma of the Ampulla of Vater*

Decade	Cases	Deaths	Mortality Rate (%)
1949–1955	1	0	0
1956–1965	5	1	20
1966–1975	11	6	54
1976–1985	15	1	6.6
Total	32	8	25

To further investigate the perioperative mortality, all factors that might influence leakage of the pancreaticojejunostomy were examined in detail. We studied leak rates by surgeon, configuration of reconstruction, anastomotic technique, quality of the pancreatic remnant, and use of ductal stents or surgical drains. Pancreaticojejunostomy leakage strongly correlated with the quality of the pancreatic remnant. In 10 patients with evidence of obstructive pancreatitis (dilated pancreatic duct, fibrosis of the pancreas as noted by the surgeon or pathologist, and/or preoperative increased serum amylase) there were no pancreaticojejunostomy leaks, while in the remaining 21 patients with a soft, normal pancreas undergoing Whipple resection (1 patient having a total pancreatectomy is excluded) the leak rate was 43%. This difference was statistically significant ($\chi^2 = 4.3$, $p < 0.05$). No other factor correlated statistically with the development of pancreaticojejunostomy breakdown. Over the past decade, only one of 15 patients developed a pancreaticojejunostomy leak, and this patient survived.

Excluding postoperative deaths, the five-year disease-free survival rate was 53% and the 10-year survival rate was 42% (Fig. 3). Median follow-up of patients who remain under active follow-up is 58 months. Fourteen patients (45%) had metastatic carcinoma involving lymph nodes in the resected specimen. These patients had a 5-year disease-free survival rate of 27% and a median survival of 37 months.

Only 12% of patients undergoing radical resection had a vagotomy added to the procedure. In almost all cases, a conservative gastrectomy (consisting only of the antrum of the stomach) was performed, such that 78% of the patients undergoing radical resection had neither a vagotomy nor an extensive (greater than 50%) gastrectomy. Although two patients developed stress upper GI hemorrhage associated with pancreaticojejunostomy leak and intra-abdominal sepsis, no patient developed symptomatic ulcers beyond the immediate postoperative period.

TABLE 3. *Causes of Operative Mortality: Radical Pancreaticoduodenectomy for Carcinoma of the Ampulla of Vater*

Complications	No. of Deaths
Pancreaticojejunostomy leak	6
Liver abscess	1
Cerebral vascular accident	1
Total	8

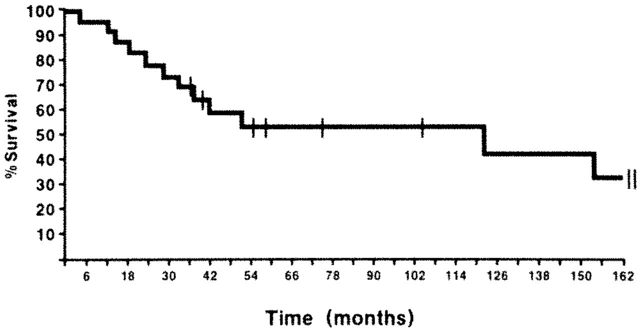
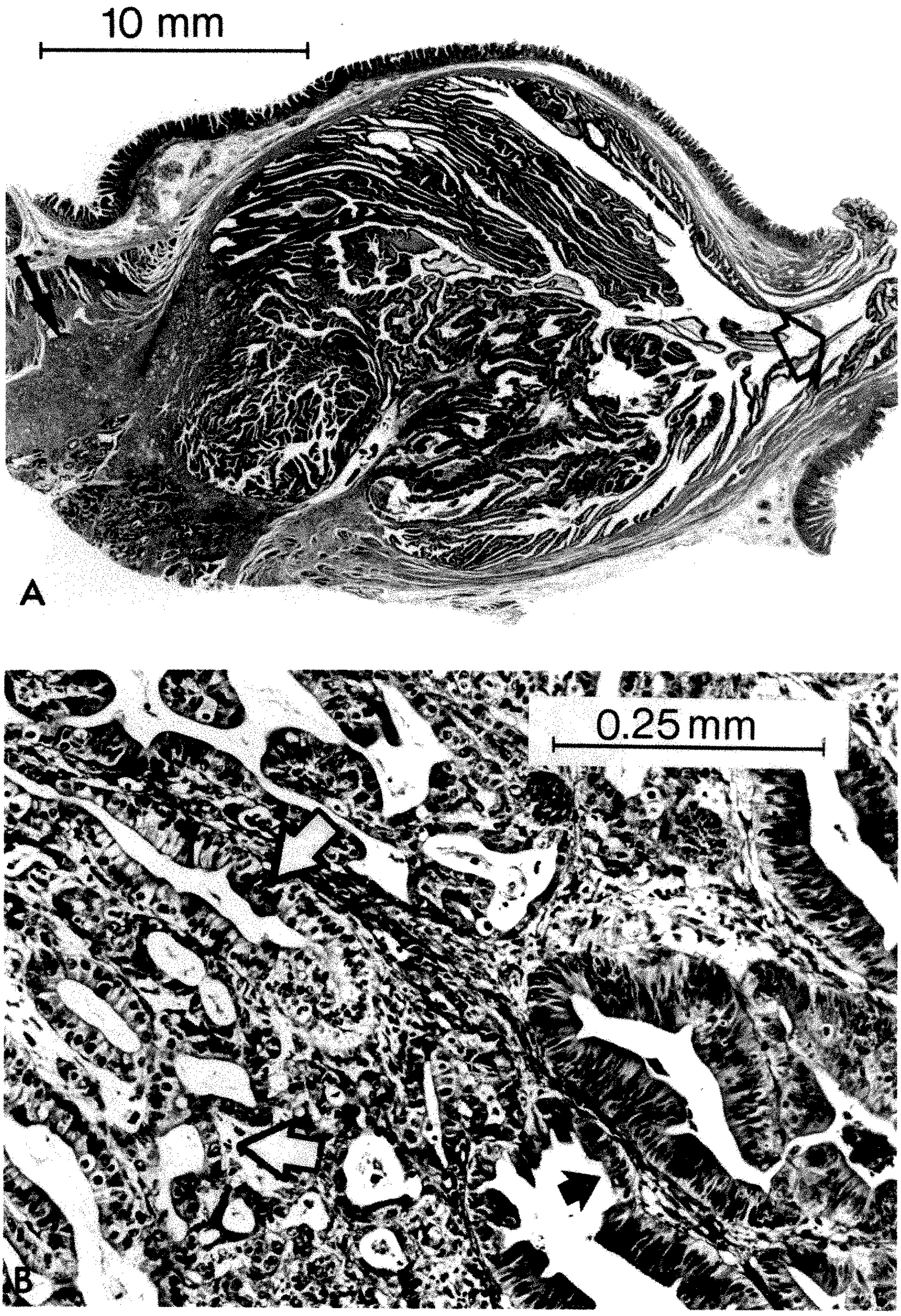


FIG. 3. Disease-free survival, patients with carcinoma of the ampulla of Vater surviving radical resection for cure. Tic marks signify the length of follow-up of patients who remain under active follow-up.

Histologically, carcinomas were classified as primarily infiltrating in 27 patients (84%) and as papillary in five patients (16%). In 11 of 31 specimens (35%) in which adequate tissue was available for detailed analysis, a benign adenomatous component was associated with the invasive carcinoma (Fig. 4A). These adenomatous components consisted of well-defined benign tubular or villous epithelial components in a broad vascularized stroma. Features of pseudostratification, increased nuclear/cytoplasmic ratio, loss of basal orientation, intraglandular budding and bridging, and increased mitoses were present in all cases to a variable degree (Fig. 4B). The presence of a benign adenomatous component correlated with size of the malignant portion of the tumor, being present in 48% (11 of 23) of patients with carcinomas less than 3 cm in size and 12% (1 of 8) in those greater than 3 cm in size.

Discussion

Diagnostic accuracy improved significantly over the course of the study with the introduction of fiberoptic upper GI endoscopy, ultrasonography, endoscopic retrograde pancreatography, and percutaneous transhepatic cholangiography. In our experience, ultrasonography has been the most helpful initial screening examination for the patient who presents with obstructive jaundice. The finding of stones within the gallbladder or common bile duct indicates the likelihood of primary biliary stone disease and suggests the need for cholecys-



FIGS. 4A and B. Microphotograph of adenoma of ampulla in association with invasive cancer. *A*. Villous tumor, with foci of carcinoma (closed arrows) (original magnification ×5). The ampullary orifice is to the right (open arrows). *B*. High power view of 4A, showing villous tumor (closed arrow) and carcinoma (open arrows) (original magnification ×250).

tectomy and common bile duct exploration without further evaluation. Stones and carcinoma of the ampulla may coexist, however, (they coincide in 12 of 37 patients in this series) underlining the importance of careful evaluation of the ampulla at the time of common duct exploration for presumed stone disease. Helpful intraoper-

TABLE 4. *Five-year Survival of Patients with Ampullary Carcinoma Surviving Pancreaticoduodenectomy*

Source	No. of Cases	5-Year Survival
		(%)
Jones et al.[3]	36	36
Warren et al.[6]	109	32
Cohen et al.[11]	22	38
Coutsoftides et al.[12]	8	50
Kellum et al.[13]	12	50
Crane et al.[14]	21	42
Grace et al.[15]	18	62
Current series	31	53

ative maneuvers include the Kocher maneuver with palpation of the ampulla, choledochoscopy, and on occasion, duodenotomy for direct visualization and biopsy of the ampulla. In addition, the preoperative finding of anemia or occult blood in the stool in a patient with biliary stone disease requires further work-up of the GI tract, including fiberoptic upper GI endoscopy with visualization of the ampulla.

Fiberoptic upper GI endoscopy has been the most accurate diagnostic test since it provides direct visualization of the ampulla of Vater and provides access for biopsy of any abnormality of the ampulla. In our experience, endoscopic retrograde cholangiopancreatography has been more productive than percutaneous transhepatic cholangiography for patients with distal common bile duct obstruction as defined by ultrasound, since it provides a direct look at the ampulla, and also provides a pancreatogram in addition to visualization of the common bile duct. This may be helpful in excluding carcinoma of the head of the pancreas by virtue of the absence of pancreatic ductal stricture.

In view of the long delay in nine patients in our series who had cholecystectomy prior to discovery of the carcinoma of the ampulla of Vater, we had hoped that the introduction of the newer diagnostic modalities would lead to a demonstrably earlier diagnosis as reflected in a more favorable stage of tumors in the latter part of our series. This however was not the case. Accurate preoperative diagnosis is still desirable, however, because it helps the surgeon to plan the operative procedure.

The 25% postoperative mortality is cause for concern. Fortunately, this mortality has been steadily declining and over the past decade has been 6.6%. Our experience of a declining mortality for pancreaticoduodenectomy parallels that of other institutions where a relatively large experience with lesions in the periampullary area can be accumulated by a relatively small number of surgeons. Better anesthesia, antibiotics, intensive care, and perioperative nutritional care have all played a role in this declining mortality, but improvement in surgical technique has been the most important factor (as evidenced by a sharp decline in pancreaticojejunostomy leaks over the past decade). The majority of these patients do not have obstruction of the duct of Wirsung with secondary changes of pancreatic ductal obstruction, pancreatitis, and pancreatic fibrosis.[8] In these cases, anastomosis of the soft pancreas, the capsule of which does not hold sutures well, is less secure. To our knowledge, this is the first report to show in a statistically significant way that the status of the pancreatic remnant strongly influences the fate of the pancreaticojejunostomy. Our efforts to provide a more secure pancreaticojejunostomy have centered around good mobilization of the transected end of the pancreatic remnant, invagination of the cut end of the pancreas into jejunum in preference to a duct to mucosa anastomosis, and use of horizontal mattress nonabsorbable sutures to lessen the chance of suture tearing through the soft pancreas resulting in dehiscence of the anastomosis.

The lack of marginal ulcer complications in this report is in conflict with the findings of Grant and Van-Heerden[9] and Scott et al.[10] In those reports a 6–36% incidence of marginal ulcer complications followed Whipple resections performed without an accompanying truncal vagotomy; furthermore, the marginal ulcers were virulent in their course and were responsible for significant morbidity and mortality. We have not experienced this complication and continue to employ conservative gastric resections without vagotomy in the majority of cases.

The 5-year disease-free survival rate is gratifying. Carcinoma of the ampulla of Vater is the most curable of all carcinomas of the upper gastrointestinal tract. Others have noted similar survival rates when reviewing carcinoma of the ampulla of Vater separate from other periampullary lesions (Table 4). In view of this relatively high surgical cure rate and the lack of effective adjuvant treatment, surgeons must be careful to maximize the cure rate by minimizing the perioperative mortality. Even in the presence of metastatic involvement of regional lymph nodes, surgical resection can be curative. Therefore, limited involvement of adjacent nodes should not preclude attempts at resection. We have not yet employed pylorus preservation in patients with carcinoma of the ampulla of Vater undergoing pancreaticoduodenectomy, out of concern that preservation of the pylorus might compromise the resection of regional nodes. However, we are following with interest recent reports suggesting that cure rates for carcinoma of the ampulla of Vater are not lessened by preserving the pylorus.[16]

The association of benign adenomas with invasive carcinoma of the ampulla has been noted by Baczako et al.[17] and Kozuka et al.[18] The known association of periampullary adenoma and carcinoma with familial polyposis syndromes and the finding in this and the previously mentioned series of a frequent association of adenoma and carcinoma of the ampulla of Vater in patients without familial polyposis suggests that an adenoma-to-carcinoma sequence may also play a role in the development of the more common nonfamilial form of carcinoma of the ampulla of Vater. Ryan et al.,[19] in a recent review, found that most duodenal villous lesions occurred at or near the ampulla of Vater. They speculated that carcinogens in the bile or pancreatic secretions might explain the finding of such a large portion of villous lesions of the ampulla in comparison to other areas of the duodenum and proximal small bowel.

Furthermore, the finding in this series that large cancers of the ampulla do not as frequently have an associated adenomatous component raises the possibility that an advancing invasive carcinoma might overgrow a precursor benign adenoma in some instances. If this assumption is correct, our finding of a benign adenoma in conjunction with invasive carcinoma in 35% of the cases would be a minimum estimate of this association. The low incidence of carcinoma of the ampulla of Vater does not make screening feasible, but the frequent association of adenoma and carcinoma in our series leads us to view with concern the occasional finding of a benign villous adenoma in the ampullary area. Because a negative endoscopic biopsy does not exclude the possibility of carcinoma within the adenoma, we believe that these should be excised in every instance. In some cases, this can be accomplished with a local resection, but Whipple resection should be carried out if the adenoma is not amenable to local resection and the patient is a good operative risk.

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Impaired Nonspecific Cellular Immunity in Experimental Cholestasis

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The abilities of polymorphonuclear leukocytes (PMN) and pulmonary alveolar macrophages (PAM), to demonstrate chemotaxis, phagocytosis, and superoxide release after bile duct ligation in the rat were investigated to determine the effect of cholestasis on nonspecific cellular immune mechanisms. Chemotactic response to C_{5a} and FMLP, phagocytosis of ^{14}C labeled *Staphylococcus aureus*, and zymosan-induced superoxide release were evaluated 21 days after bile duct ligation (BDL), sham operation, or in normal controls. Serum total bilirubin level was elevated after BDL ($p < 0.01$). Chemotactic ability was similar to each group. PMN phagocytic uptake of ^{14}C labeled *Staphylococcus aureus* was depressed in BDL ($p < 0.05$). BDL rats exhibited impaired PAM phagocytic indices and improved PMN superoxide release ($p < 0.03$). PAM superoxide release was similar in each study group. Alterations in phagocytic function with cholestasis are important deficits in nonspecific cellular immunity that may contribute to the high incidence of infective complications associated with obstructive jaundice.

SEVERAL CLINICAL STUDIES have reported a high incidence of infective complications in patients with obstructive jaundice.[1-7] The majority of such infective sequelae are due to enteric bacteria or their liberated toxins that result in the development of ascending cholangitis, septicemia, endotoxemia, and intra-abdominal sepsis in the cholestatic host.[7] The basis for this predisposition to infective complications is not understood, but may be due to alterations in nonspecific host defense mechanisms. Previous studies have demonstrated impaired reticuloendothelial function in patients and animals with obstructive jaundice.[8-10] However, little is known of the effect of cholestasis on extrahepatic, nonspecific cellular immune function. In this study, we investigated the ability of polymorphonuclear leukocytes (PMN) and pulmonary alveolar macrophages (PAM) isolated from cholestatic rats to demonstrate directed migration, phagocytosis, and superoxide release, critical in the elimination of invading bacterial pathogens.

Materials and Methods

Animals

Female Sprague-Dawley (SD) rats weighing 200–250 g (Timco Laboratories, Houston, TX) were housed in cages of five and subjected to a 12-hour alternate light-dark cycle. Throughout the study rats were fed standard rat chow (Purina Formulab 5008) and allowed water *ad libitum.* Animals were assigned to one of three groups: bile duct ligation (BDL), sham operation (Sham), and normal control (NC). Twenty-one days after operation the animals were killed and PMN and PAM populations obtained as described below.

Bile Duct Ligation

This was performed under ether anesthesia on the first day of the study: a central upper abdominal incision was made, the common bile duct identified, doubly ligated with two 3-0 silk ligatures, and divided.[11] High bile duct ligation was performed in the same position in all animals. In those animals undergoing sham operation, the common bile duct was identified and freed from the surrounding tissue only.

Serum Biochemistry and Histology

Serum total bilirubin determinations were performed in BDL, Sham, and NC groups at days 0 and 21 by the

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Walters and Gerarde method.[12] Liver histology (H and E stain) was performed on livers excised from study animals at the time of sacrifice (Department of Pathology, University of Texas Medical School, Houston, Texas).

Cell Isolation

Polymorphonuclear leukocytes were obtained by giving rats an IP injection of 15 ml of 12% sodium caseinate 16 hours prior to sacrifice. The following day PMN were harvested from the peritoneal cavity by saline lavage. They were washed, pooled, and handled in a manner similar to that described below for PAM. Pulmonary macrophages were harvested from BDL, Sham, and NC rats by bronchopulmonary lavage on the day of sacrifice. Briefly, after rats were anesthetized with sodium pentobarbital (30 mg/rat), the abdominal aorta was severed and the trachea cannulated. Sodium chloride solution (7 mL of 0.9% solution) was instilled and removed seven times. The cells obtained following centrifugation and washing were greater than 95% PAM or PMN and all groups were 95% viable. Cells were then used either as suspensions (chemotaxis) or as monolayers (superoxide release and phagocytosis) prepared as described by Mitchell and coworkers.[13]

Chemotaxis

The chemoattractants included the synthetic tripeptide FMLP (Sigma Biochemicals, St. Louis, MO) at final concentration of 10^{-8} M and 10% C_{5a} activated serum, prepared by incubating homologous rat serum with zymosan particles at 37 C for 15–60 min. The attractant was added to the lower half of modified Boyden chambers containing M199 and 0.1% albumin. The upper half of the chamber contained 1.5×10^6 PMN or PAM harvested from BDL, Sham, or NC rats and suspended in medium (M) 199 containing 0.1% albumin. Control chambers contained only M199 and albumin in the lower half to assess random migration. The upper and lower halves of the chambers were separated by either an 8-μm (PAM) or 5-μm (PMN) pore, gelatin-coated polycarbonate filter (Nucleopore Corp., Pleasanton, CA). After the chambers were incubated for 2 hours at 37 C in 95% air and 5% CO_2, the filters were removed, fixed, stained, mounted on glass slides, and allowed to dry overnight before placing coverslips.[14] Migration was assessed by enumerating the PAM or PMN that had moved through the filter in 15 randomly selected oil power fields (×1000).

Phagocytosis of Labeled Bacteria

The live bacterial particle was used at levels consistent with biological reality (10 bacteria/macrophage). Monolayers consisting of 3×10^6 cells (when added) were formed on plastic surfaces at 37 C as previously described.[13] After 1 hour, the approximate 35% of cells that were nonadherent were washed off. Fresh Hank's balanced salt solution containing glucose (1 mg/mL) was added to the monolayers followed by the ^{14}C-labeled *Staphylococcus aureus* (strain 209P) at a multiplicity of 10 bacteria/phagocyte. At the indicated time, the particles were removed; the monolayers were vigorously washed in saline and dried in preparation for counting. Zero time counts were subtracted from subsequent measurements to account for bacterial adherence.[15] Protein determinations were performed on the monolayers as well as on the bacteria to express final results as micrograms of *S. aureus* ingested per milligram of monolayer protein.

Superoxide Release

Superoxide release was measured on monolayers consisting of 3.0×10^6 PAM as previously described.[16] Superoxide-dependent cytochrome C reduction was determined spectrophotometrically at 550 nm in the presence or absence of superoxide dismutase (Sigma Chemicals, St. Louis, MO). Measurements were performed both on cells at rest and following phagocytosis of opsonized zymosan. Zymosan particles were opsonized by initially suspending them in 0.9% saline, washing them and then incubating them with rat serum for 30 minutes. Following opsonization, it was stored, refrigerated, and used as a suspension when needed.

Bacterial Cultures

Samples of blood and bile were taken asceptically from BDL, Sham, and NC animals at the time of sacrifice and innoculated into 3.5 mL of Schaedler's broth (BBL, Cockeyville, MD, USA). Samples of broth were incubated aerobically at 37 C. Culture media was then checked for bacterial growth at 24 hours, 48 hours, and 5 days following incubation.

Statistical Analysis

All results were expressed as mean ± SD and Student's unpaired t-test was used for statistical analysis. A p value <0.05 was considered to be statistically significant.

Results

Serum Biochemistry and Histology

Initial serum total bilirubin levels in BDL, Sham, and NC groups were 0.2 ± 0.1, 0.2 ± 0, and 0.2 ± 0.1 mg/dL, respectively. Twenty-one days following operation, hyperbilirubinemia was evident in BDL animals compared to Sham and NC groups 6.3 ± 2.9 *versus* 0.03 ± 0.1 and 0.1 ± 0 mg/dL ($p < 0.01$).

TABLE 1. *Chemotactic Response to C_{5a} and FMLP in BDL, Sham, and Normal Control Groups**

	Polymorphonuclear Leukocyte			Pulmonary Macrophage		
Treatment	M199	FMLP	C_{5a}	M199	FMLP	C_{5a}
BDL	16.8 ± 5.3	43.5 ± 14.1	43.5 ± 19.8	12.3 ± 3.2	31.0 ± 4.2	34.5 ± 9.2
Sham	20.5 ± 2.8	39.8 ± 11.7	43.5 ± 14.5	10.5 ± 0.7	29.5 ± 2.8	27.0 ± 4.2
Normal control	16.5 ± 2.1	33.0 ± 1.4	33.0 ± 1.4	10.3 ± 2.5	28.3 ± 8.1	28.0 ± 8.5

* Chemotaxis on pooled samples (N = 10) was measured in modified Boyden chambers with either 10^{-8} M FMLP or 10% C_{5a} activated serum as the chemoattractants. PMNs or pulmonary macrophages were placed in the upper compartments of the chamber in M199 with 0.1% albumin. Either M199 (random migration) or attractant (chemotaxis) was added to the lower compartment. Results expressed as the mean number of migratory cells per 15 oil power fields ± SD. Differences between BDL, Sham, and Normal Control groups are not statistically significant.

Liver histology revealed bile duct proliferation and portal venule distension in BDL animals at the time of sacrifice. Minimal changes of peripheral fibrosis and hepatocyte swelling were also apparent in BDL animals.

Bacteriologic Changes

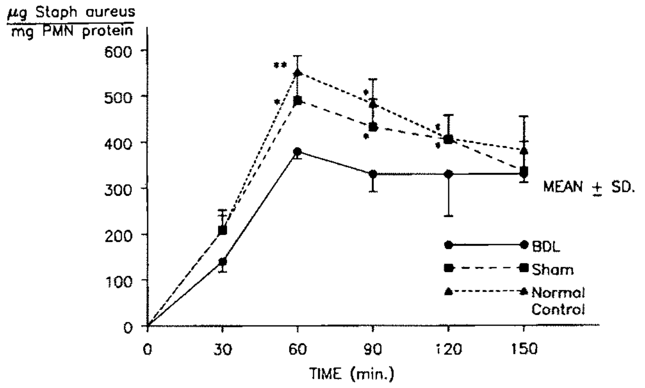
Aerobic and anaerobic cultures of blood and bile derived from experimental animals were sterile 1, 2, and 5 days following sample incubation.

Chemotactic Response to C_{a5} Activated Serum and FMLP

Random migration of PMNs showed no difference between BDL, Sham, and NC rats (Table 1). A satisfactory chemotactic response to C_{5a} activated serum and FMLP was seen in BDL rats, compared to Sham and NC animals in duplicate experiments. Similarly, experiments of PAM chemotactic response demonstrated effective migratory capacity in the BDL group compared to control animals (Table 1).

Phagocytosis of ^{14}C Labeled Bacteria

Polymorphonuclear leukocytes isolated from BDL animals demonstrated a diminished phagocytic ability to ingest ^{14}C labelled *S. aureus* at 30, 60, 90, 120, and 150 minutes compared to PMNs isolated from Sham and NC animals (Fig. 1). This effect was routinely demonstable in consecutive experiments. Similarly, kinetic studies of PAM phagocytic activity demonstrated reduced ingestive capacity in cells isolated from cholestatic animals compared to those obtained from control rats. Although serial studies consistently demonstrated deterioration of PAM phagocytic capacity in cholestatic animals, interassay variation of phagocytic indices was such that results are expressed as individual experiments rather than composite data.



*p<0.04 **p<0.001 compared to BDL.

FIG. 1. Polymorphonuclear leukocyte uptake of ^{14}C labeled *Staphylococcus aureus* at selected time intervals. Results represent two separate experiments performed on pooled samples (N = 5) from each group. Each determination was performed in duplicate and results expressed as mean ± SD.

There was uniform diminution of PAM phagocytic indices in each of three individual experiments (Fig. 2). In view of the small number of animals (N = 3) and the interassay variability of the phagocytic indices between these studies, we were unable to demonstrate statistically significant differences between study groups using both parametric and nonparametric statistical analysis. Each experiment demonstrated that PAM phagocytic indices varied from 50–80% of control values and were consistently suboptimal in comparison with normal control and sham groups. These observations suggest impairment of PAM phagocytic mechanisms in addition to those of the neutrophil.

Superoxide Release in Response to Zymosan Stimulation

Polymorphonuclear leukocytes isolated from cholestatic animals demonstrated increased superoxide release compared to those harvested from Sham and NC groups (Table 2). Duplicate experiments also revealed a tendency for Sham PMNs to release more superoxide than those obtained from NC animals, although the differences were not statistically significant ($p < 0.06$). This may be attributable to the effect of operative stress on PMN metabolism. Triplicate experiments on PAM superoxide metabolism suggested enhanced radical release in the Sham group, compared to BDL and NC animals, although the differences observed were not statistically significant (Table 3).

Discussion

Infective complications are commonly seen in patients with extrahepatic cholestasis;[1-7] however, little is known of the effect of cholestasis on host immune status. Previous work from our group using this BDL rat model has shown depressed responsiveness to phytohemagglutinin (PHA) mitogen and allogeneic F_{344} antigen *in vivo* and *in vitro* 21 days after the onset of obstructive jaundice, suggesting that specific cell mediated immunity is impaired.[17] Integrity of systemic and local nonspecific cellular immune mechanisms are essential in the host's defense against invading bacterial pathogens. Impairment of this component of host defense may therefore account for the high incidence of bacterial infections reported in these patients. Studies have demonstrated a diminished survival rate in BDL rats compared to Sham operated animals following experimental peritonitis.[18] This suggests an impaired effector response to bacterial infection *in vivo* in cholestatic animals.

Additional studies have demonstrated impaired Kupffer cell function in the bile duct obstructed host.[8-11] Little is known, however, of the integrity of extrahepatic, nonspecific cellular immune mechanisms in the cholestatic host, critical in the control and elimination of bacterial pathogens. In order for a phagocyte to be effectively involved in host defense it must be able to (1) localize microorganisms through its ability to demonstrate directed migration or chemotaxis; (2) engulf or phagocytose the microorganism; and (3) alter its own cellular metabolism to produce reactive oxygen metabolites with microbicidal properties. Our study attempts to assess each of these critical steps by evaluating PMN and PAM function during experimental biliary obstruction in the rat.

The ability of phagocytes to demonstrate directed migration *in vitro* to FMLP and C_{5a} was unaffected in this experimental model, suggesting integrity of this critical mechanism in the cholestatic host. The most dramatic effect of cholestasis was to inhibit the normal phagocytic uptake of ^{14}C labeled *S. aureus* by isolated PMN and PAMs. This inhibitory effect was consistently seen throughout the entire 150-minute incubation period in serial experiments. This suppression of phagocytic ability suggests a critical impairment of systemic and local nonspecific cellular immune mechanisms in the cholestatic host. Such alterations in phagocytic capacity may exist in cholestatic animals *in vivo* and would explain the high mortality noted in cholestatic animals following severe infective stress.[18] The basis for impaired phagocytosis in cholestatic animals remains unknown. Serum inhibitory factors may be present in cholestatic sera that block normal phagocytic mechanisms either directly or through action on the complement system or serum opsonins. Increased concentrations of serum bilirubin and bile salts may be important in this respect and further consideration of their role in suppressing normal PMN and PAM phagocytic activity warrants investigation.[19-21] Further studies also are required to examine phagocytic function *in vivo* in cholestatic animals.

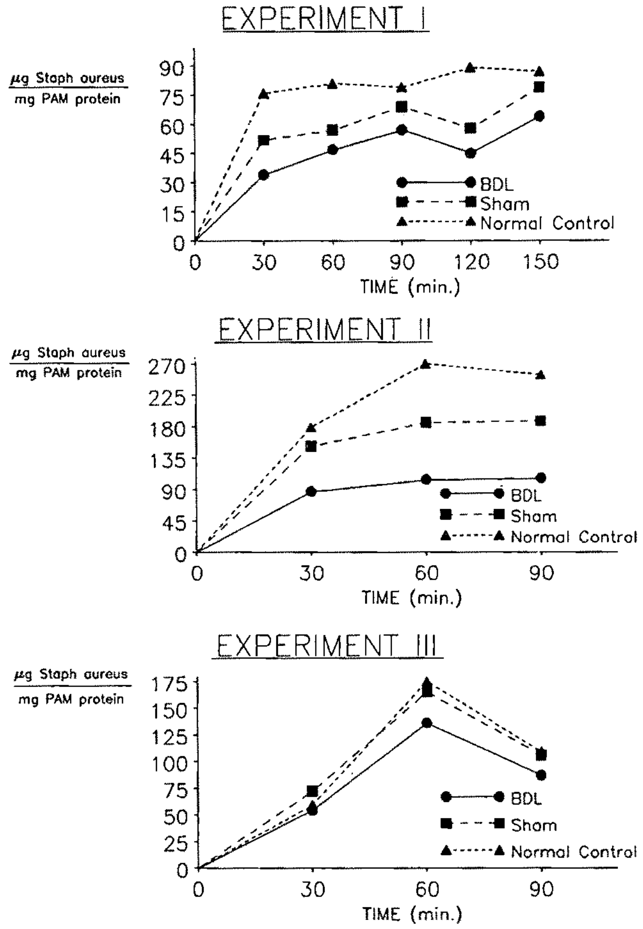


FIG. 2. Pulmonary macrophage uptake of ^{14}C labeled *Staphyloccus aureus* at selected time intervals in three separate experiments. Each experiment was performed on pooled samples (N = 8) from each group and each determination performed in duplicate to obtain mean values.

Studies invesigating superoxide metabolism consistently demonstrated enhanced PMN superoxide release in cholestatic animals compared to control groups. Furthermore, PMNs isolated from Sham rats released more superoxide than NC animals, suggesting that operative intervention alone augments PMN superoxide release.

TABLE 2. *Polymorphonuclear Leukocyte Superoxide Release in BDL, Sham, and Normal Control Groups**

Group	Superoxide Release
BDL	21.9 ± 2.2
Sham	10.7 ± 2.3†
Normal	4.0 ± 0.1‡

* Results are expressed as nanomoles of zymosan-stimulated superoxide release per milligram of cell protein in 30 minutes. The values represent the mean ± SD of two separate experiments on pooled samples (N = 5), each determination performed in duplicate.

† $p < 0.005$.

‡ $p < 0.003$ compared with BDL.

TABLE 3. *Pulmonary Macrophage Superoxide Release in BDL, Sham, and Normal Control Groups**

	Group	Superoxide Release
Experiment I	BDL	6.3 ± 2.3
	Sham	14.8 ± 2.8
	Normal Control	7.7 ± 1.8
Experiment II	BDL	8.9 ± 1.1
	Sham	11.1 ± 0.9
	Normal Control	12.2 ± 2.2
Experiment III	BDL	23.4 ± 3.0
	Sham	45.3 ± 5.2
	Normal Control	15.9 ± 1.3
Combined results of experiments I, II, and III	BDL	12.9 ± 9.2
	Sham	23.7 ± 18.7
	Normal Control	11.9 ± 4.1

* Results are expressed as nanomoles of zymosan-stimulated superoxide released per milligram of cell protein in 30 minutes. The values represent the mean ± SD of pooled samples from each experimental group (N = 6), each determination performed in duplicate.

Pulmonary macrophage superoxide release did not appear to be affected by coexisting cholestatis, although PAMs isolated from Sham animals again demonstrated increased superoxide release compared to BDL and NC groups. The basis of the differential effect of cholestatis on PMN and PAM superoxide release remains unknown, but may reflect inherent metabolic differences between the two cell populations. For example, it is well known that PAMs rely more on oxidative sources and mitochondrial respiration than PMNs, where functional processes are almost completely dependent on glycolysis.[22]

Alterations in PMN and PAM phagocytic ability and superoxide release associated with liver dysfunction may represent a critical degradation of nonspecific immune mechanisms in the cholestatic host. Improvement of liver function by therapeutic decompressive biliary drainage may have a therapeutic role in improving such impairments in PAM and tissue macrophage phagocytic capacity. Subsequent improvements of host defense may accordingly diminish the susceptibility of the cholestatic host to infective complications. It is of interest that Vane et al. demonstrated that prolonged periods of internal biliary drainage were required to reverse impaired Kupffer cell phagocytic function associated with biliary obstruction, despite the prompt improvement in liver function with drainage.[23] Further studies investigating the relative efficacy of internal and external biliary drainage in restoring host immune status are also required to determine the respective benefits of such procedures in lessening infective morbidity associated with obstructive jaundice.

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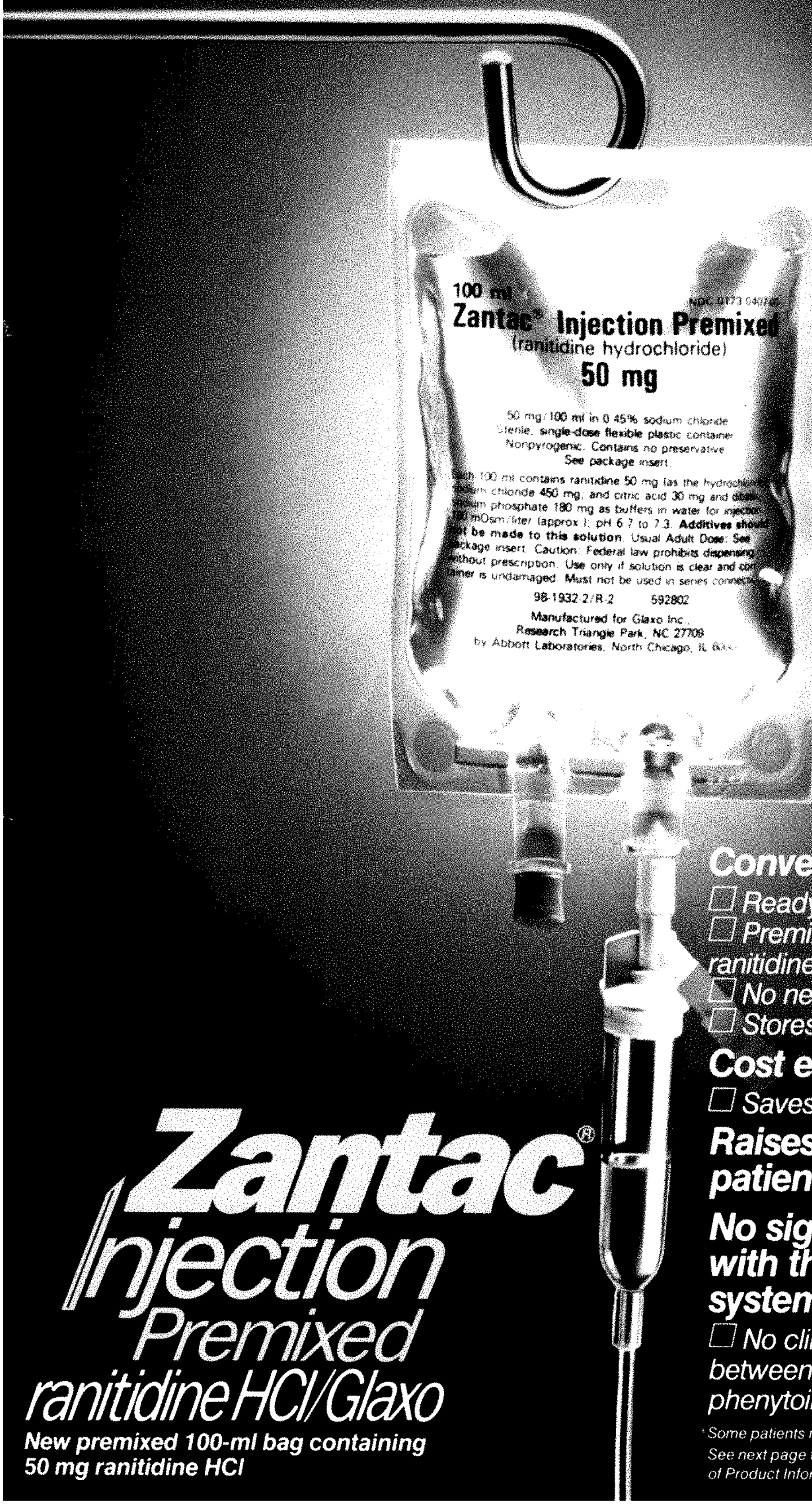
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See next page for brief summary of Product Information.

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The following is a brief summary only. Before prescribing, see complete prescribing information in ZANTAC® Injection/ZANTAC® Injection Premixed product labeling.
INDICATIONS AND USAGE: ZANTAC® Injection and ZANTAC® Injection Premixed are indicated in some hospitalized patients with pathological hypersecretory conditions or intractable duodenal ulcers, or as an alternative to the oral dosage form for short-term use in patients who are unable to take oral medication.
CONTRAINDICATIONS: ZANTAC® Injection and ZANTAC® Injection Premixed are contraindicated for patients known to have hypersensitivity to the drug.
PRECAUTIONS: General: 1. Symptomatic response to ZANTAC® therapy does not preclude the presence of gastric malignancy.
2. Since ZANTAC is excreted primarily by the kidney, dosage should be adjusted in patients with impaired renal function (see **DOSAGE AND ADMINISTRATION**). Caution should be observed in patients with hepatic dysfunction since ZANTAC is metabolized in the liver.
3. In controlled studies in normal volunteers, elevations in SGPT have been observed when H_2-antagonists have been administered intravenously at greater than recommended doses for five days or longer. Therefore, it seems prudent in patients receiving IV ranitidine at doses greater than or equal to 100 mg qid for periods of five days or longer to monitor SGPT daily (from day 5) for the remainder of IV therapy.
Laboratory Tests: False-positive tests for urine protein with Multistix® may occur during ZANTAC therapy, and therefore testing with sulfosalicylic acid is recommended.
Drug Interactions: Although ZANTAC has been reported to bind weakly to cytochrome P-450 in vitro, recommended doses of the drug do not inhibit the action of the cytochrome P-450-linked oxygenase enzymes in the liver. However, there have been isolated reports of drug interactions that suggest that ZANTAC may affect the bioavailability of certain drugs by some mechanism as yet unidentified (eg, a pH-dependent effect on absorption or a change in volume of distribution).
Pregnancy: *Teratogenic Effects: Pregnancy Category B:* Reproduction studies have been performed in rats and rabbits at oral doses up to 160 times the human oral dose and have revealed no evidence of impaired fertility or harm to the fetus due to ZANTAC. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.
Nursing Mothers: ZANTAC is secreted in human milk. Caution should be exercised when ZANTAC is administered to a nursing mother.
Pediatric Use: Safety and effectiveness in children have not been established.
ADVERSE REACTIONS: Transient pain at the site of intramuscular injection has been reported. Transient local burning or itching has been reported with intravenous administration of ZANTAC® Headache, sometimes severe, seems to be related to ZANTAC administration. Constipation, diarrhea, nausea/vomiting, and abdominal discomfort/pain have been reported. There have been rare reports of malaise, dizziness, somnolence, insomnia, vertigo, tachycardia, bradycardia, premature ventricular beats, and arthralgias. Rare cases of reversible mental confusion, agitation, depression, and hallucinations have been reported, predominantly in severely ill elderly patients. Rare cases of reversible blurred vision suggestive of a change in accommodation have been reported.

In normal volunteers, SGPT values were increased to at least twice the pretreatment levels in 6 of 12 subjects receiving 100 mg qid IV for seven days, and in 4 of 24 subjects receiving 50 mg qid for five days. With oral administration there have been occasional reports of reversible hepatitis, hepatocellular or hepatocanalicular or mixed, with or without jaundice.

Reversible blood count changes (leukopenia, granulocytopenia, and thrombocytopenia) have occurred in a few patients. Rare cases of agranulocytosis or of pancytopenia, sometimes with marrow hypoplasia, have been reported.

Although controlled studies have shown no antiandrogenic activity, occasional cases of gynecomastia, impotence, and loss of libido have been reported in male patients receiving ZANTAC, but the incidence did not differ from that in the general population.

Incidents of rash, including rare cases suggestive of mild erythema multiforme, and, rarely, alopecia, have been reported, as well as rare cases of hypersensitivity reactions (eg, bronchospasm, fever, rash, eosinophilia) and small increases in serum creatinine.
OVERDOSAGE: Information concerning possible overdosage and its treatment appears in the full prescribing information.
DOSAGE AND ADMINISTRATION: (See complete prescribing information in ZANTAC® Injection/ZANTAC® Injection Premixed product labeling.)
Dosage Adjustment for Patients with Impaired Renal Function: On the basis of experience with a group of subjects with severely impaired renal function treated with ZANTAC, the recommended dosage in patients with a creatinine clearance less than 50 ml/min is 50 mg every 18 to 24 hours. Should the patient's condition require, the frequency of dosing may be increased to every 12 hours or even further with caution. Hemodialysis reduces the level of circulating ranitidine. Ideally, the dosage schedule should be adjusted so that the timing of a scheduled dose coincides with the end of hemodialysis.
HOW SUPPLIED: ZANTAC® Injection, 25 mg/ml, containing phenol 0.5% as preservative is available as follows:
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(NDC 0173-0363-39) 10-ml multidose vials (Singles)

Store below 30°C (86°F). Protect from light.

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Exposure of pharmaceutical products to heat should be minimized. Avoid excessive heat. Protect from freezing. It is recommended that the product be stored at room temperature (25°C); however, brief exposure up to 40°C does not adversely affect the product.

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Indications: For control of severe nausea and vomiting

Contraindications: Comatose or greatly depressed states due to C.N.S. depressants; pediatric surgery; use in children under 2 years of age or under 20 lbs.; use in children for conditions for which dosage has not been established

Warnings: The extrapyramidal symptoms which can occur secondary to 'Compazine' may be confused with the central nervous system signs of an undiagnosed primary disease responsible for the vomiting, e.g., Reye's syndrome or other encephalopathy. The use of 'Compazine' and other potential hepatotoxins should be avoided in children and adolescents whose signs and symptoms suggest Reye's syndrome.

May cause tardive dyskinesia in some patients on neuroleptic (antipsychotic) therapy, usually long-term. This syndrome consists of potentially irreversible, involuntary dyskinetic movements. The risk of tardive dyskinesia and likelihood of irreversibility are thought related to duration of treatment and total cumulative dose of neuroleptic drugs.

Use in patients with bone marrow depression only when potential benefits outweigh risks. Patients who develop a hypersensitivity reaction (e.g., blood dyscrasias or jaundice) to a phenothiazine generally should not be reexposed to any phenothiazine. Caution patients about activities requiring alertness (e.g., operating vehicles or machinery), especially during the first few days' therapy. Prochlorperazine may intensify or prolong the action of other C.N.S. depressants.

Use in pregnancy is not recommended except in cases so serious and intractable that, in the physician's judgment, drug intervention is required and potential benefits outweigh possible hazards. There have been instances of prolonged jaundice, extrapyramidal signs, hyperreflexia or hyporeflexia in newborn infants whose mothers received phenothiazines. There is evidence that phenothiazines are excreted in the breast milk of nursing mothers.

Precautions: The antiemetic action of 'Compazine' may mask the signs and symptoms of overdosage of other drugs and may obscure the diagnosis and treatment of other conditions such as intestinal obstruction, brain tumor and Reye's syndrome (See Warnings). Postoperative aspiration of vomitus has occurred in a few surgical patients who received prochlorperazine as an antiemetic. When used concomitantly with cancer chemotherapeutic drugs, may obscure vomiting as a sign of these agents' toxicity. Deep sleep and coma have been reported with prochlorperazine, usually with overdosage.

Neuroleptic drugs cause elevated prolactin levels that persist during chronic administration. Since approximately one-third of human breast cancers are prolactin-dependent *in vitro*, this elevation is of potential importance if neuroleptic drug administration is contemplated in a patient with a previously detected breast cancer. Neither clinical nor epidemiologic studies to date, however, have shown an association between the chronic administration of neuroleptic drugs and mammary tumorigenesis

Permanently stop neuroleptic therapy if neuromuscular reactions occur in pregnant women or in children.

In children with acute illnesses or dehydration, use only under close supervision. Avoid high doses and parenteral administration when cardiovascular system is impaired since hypotension has occurred. Use cautiously in patients with glaucoma. Use with caution in persons who will be exposed to extreme heat since phenothiazines may interfere with thermoregulatory mechanisms. Phenothiazines can diminish the effect of oral anticoagulants. Phenothiazines can produce alpha-adrenergic blockade. Thiazide diuretics may accentuate orthostatic hypotension that may occur with phenothiazines. Antihypertensive effects of guanethidine and related compounds may be counteracted when phenothiazines are used concomitantly. Concomitant administration of phenothiazines with propranolol results in increased plasma levels of both drugs and may also precipitate phenytoin toxicity. Phenothiazines may lower the convulsive threshold; dosage adjustments of anticonvulsants may be necessary. Presence of phenothiazines may produce false positive phenylketonuria (PKU) test results. Patients should not receive 'Compazine' 48 hours before or 24 hours after myelography with the contrast medium metrizamide.

Adverse Reactions: Drowsiness, dizziness, amenorrhea, blurred vision, skin reactions. Hypotension. Cholestatic jaundice, leukopenia, agranulocytosis. Fatty changes in the liver have been observed in a few patients who died while receiving the drug (no causal relationship has been established). Neuromuscular (extrapyramidal) reactions: motor restlessness, dystonias, pseudo-parkinsonism, tardive dyskinesia, and a variant, tardive dystonia. Contact dermatitis is a possibility if 'Compazine' Injection (solution) inadvertently gets on hands or clothing.

Other adverse reactions reported with 'Compazine' or other phenothiazines: Some adverse effects are more frequent or intense in specific disorders (e.g., severe hypotension in mitral insufficiency or pheochromocytoma). Grand mal and petit mal convulsions; altered cerebrospinal fluid proteins; cerebral edema; prolongation and intensification of the action of C.N.S. depressants, atropine, heat and organophosphorus insecticides; dryness of mouth, nasal congestion, headache, nausea, constipation, obstipation, adynamic ileus, ejaculatory disorders/impotence, priapism, atonic colon, urinary retention, miosis and mydriasis; reactivation of psychotic processes, catatonic-like states, hypotension (sometimes fatal); cardiac arrest; pancytopenia, thrombocytopenic purpura, eosinophilia, hemolytic anemia, aplastic anemia; biliary stasis; hyperglycemia, hypoglycemia, glycosuria, lactation, galactorrhea, gynecomastia, menstrual irregularities, false positive pregnancy tests; photosensitivity, itching, erythema, urticaria, eczema up to exfoliative dermatitis, asthma, laryngeal edema; angioneurotic edema, anaphylactoid reactions; peripheral edema; reversed epinephrine effect; hyperpyrexia, mild fever after large I.M. doses; increased appetite; increased weight; a systemic lupus erythematosus-like syndrome; pigmentary retinopathy; neuroleptic malignant syndrome, which may be fatal; with prolonged administration of substantial doses, skin pigmentation, epithelial keratopathy, and lenticular and corneal deposits.

EKG changes have been reported. Discontinue long-term, high-dose therapy gradually.

Note: Sudden death in patients taking phenothiazines (apparently due to cardiac arrest or asphyxia due to failure of cough reflex) has been reported.

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Parietal Cell Vagotomy as an Emergency Procedure for Bleeding Peptic Ulcer

JACK HOFFMANN, M.B., F.C.S.(S.A.), F.R.C.S.(ED), AGNETE DEVANTIER, M.D., TINA KOELLE, M.D., and HANS-ERIC JENSEN, M.D., PH.D.

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Twenty-three selected patients presenting with massive bleeding from peptic ulcers underwent emergency parietal cell vagotomy (PCV). Ninteen patients had a duodenal ulcer, two a prepyloric ulcer, and one a gastric ulcer. The patients were studied retrospectively with regard to postoperative mortality and morbidity, early rebleeding, and recurrent ulceration. Two patients (9%) died after operation, one of rebleeding. No others suffered rebleeding. One further patient had major respiratory complications and 14 others developed minor complications. The remaining 21 patients were followed for between 2 and 72 months. Two patients (10%) developed recurrent ulcers. The authors conclude that parietal cell vagotomy may be used as an emergency operation for bleeding peptic ulcer in selected cases with an acceptably low mortality, rebleeding rate, and incidence of recurrent ulceration.

ALTHOUGH EMERGENCY PARIETAL cell vagotomy (PCV) for bleeding peptic ulcer was introduced by Professor David Johnston in 1973,[1,2] there have been only sporadic reports of its use for this indication from other surgeons in the intervening 14 years.[3-7] Of these, only two papers describe more than a few cases.[3,5] We have therefore undertaken a retrospective study of 23 patients who have undergone emergency PVC for massive bleeding from a peptic ulcer.

Patients and Methods

In a 6-year period from 1980 to 1986, 50 patients were operated on for massive bleeding from a peptic ulcer. Of these, 23 underwent PCV as an emergency procedure. The remainder had some other operation because their general condition indicated a more rapid procedure than PCV, because local conditions rendered PCV inexpedient, or because the surgeon considered a gastrectomy more appropriate. These 27 patients are not considered further.

Of the 23 patients undergoing PCV, 21 were men and two were women. Their ages ranged from 38–88 years with a mean of 62 years. Seven patients were aged 70 years and older. Twelve patients showed signs of shock or impending shock. Their preoperative and operative blood transfusion requirement ranged from 1 to 9 L (mean 6 L). Eleven had moderate chronic cardiopulmonary disease while the others were considered to be in good general condition.

Twenty patients had duodenal ulcers and two prepyloric ulcers. In one patient who had multiple gastric ulcers plus a duodenal ulcer, the bleeding source was one of the gastric ulcers.

The ulcers were approached in the following way in order to accomplish transfixion of the bleeding source: Nineteen had a longitudinal duodenotomy only. In 10 this was closed longitudinally and in nine, transversely. Two patients had gastrotomies only. One patient had a pyloroduodenotomy that was closed longitudinally without performing a pyloroplasty. In one patient the access is not described. All patients then underwent a PCV without a drainage procedure.

The patients were studied retrospectively with regard to operative mortality and morbidity, early rebleeding, and ulcer recurrence.

Results

One patient died after surgery from rebleeding after refusing reoperation. No other patient rebled. A second patient died from cardiac complications. One further patient had major respiratory complications but sur-

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vived. Fourteen other patients had minor cardiac or respiratory complications, wound infection, urinary infection, or bacteremia from intravenous catheters.

The surviving 21 patients were followed for between 2 and 72 months (mean: 24 months) by personal interview, telephone, or by written questionnaire. One patient died 3 months after surgery of unrelated causes without evidence of rebleeding or recurrent ulceration. A second patient developed a gastroscopically proven recurrent ulcer with gastric retention and was reoperated 2 months after the original operation. The gastric retention was not due to the patient's duodenotomy. A third patient developed signs of gastric retention, refused any further investigation or surgery, and is being treated on long-term cimetidine and metacloplamide. His duodenotomy had been closed transversely. This patient has been regarded as having a recurrent ulcer but this has never been proved. A denervated pylorus may be the explanation for his symptoms. The 19 remaining patients have no symptomatic evidence of recurrent ulceration. The ulcer recurrence rate was thus two of 21 patients (10%). Both recurrences were among the patients with duodenal ulcers.

The single patient who had undergone a pyloric transection did not develop gastric retention.

Discussion

Although endoscopic methods of hemostasis are now being evaluated,[8,9] in most centers massive or recurrent bleeding from a duodenal ulcer demands surgical treatment. The choice then lies between vagotomy and antrectomy, and vagotomy alone. When considering which of the alternatives to choose, one must consider mortality and morbidity, incidence of early rebleeding, recurrent ulceration, and long-term postgastrectomy or postvagotomy side effects. Vagotomy and antrectomy has the advantage of having a lower recurrence rate than vagotomy alone, but this is outweighed by the higher mortality, morbidity, and incidence of long-term side effects following a procedure involving gastrectomy.[10] There is some evidence that the early rebleeding rate is lower after vagotomy and antrectomy than after vagotomy alone,[11,12] but acceptably low secondary hemorrhage rates are also reported following the latter procedure.[1-3]

If one, for the above reasons, chooses to do a vagotomy alone rather than a vagotomy plus antrectomy for the emergency treatment of bleeding duodenal ulcer, should this be a truncal vagotomy (TV) or a PCV? The main disadvantage of PCV in the acute situation is that it takes 30 minutes longer to perform than a TV,[1,2] which may be a drawback in these patietns who are often elderly, shocked, and suffering from concomitant diseases. A further detrimental aspect is that PCV will be followed by a higher incidence of recurrent ulceration than TV.[13] On the other side of the coin, PCV has a lower morbidity, mortality, and incidence of postvagotomy complications than TV at least in the elective situation.[13] A comparison of these complications in the emergency situation has not been published. If one considers that it is easier to treat a recurrent ulcer than severe postvagotomy symptoms, one might be tempted to opt for PCV rather than TV. Selective gastric vagotomy and drainage may be done for bleeding ulcers with a low mortality but with a relatively high rebleeding rate of 13.5%.[12]

Although Johnston originally reported 10 consecutive and therefore presumably unselected cases of PCV used for acute bleeding,[1] he subsequently states that one should not hesitate to do a TV in poor risk patients.[2] In the light of this selection, 65% of Johnston's patients underwent PCV and the rest TV. In our series half the patients had PCV. This attitude of selection of patients is echoed by others who advocate PCV in the patient with acute bleeding.[4,5,7] Relative contraindications to PCV when the more rapid TV should be chosen are old, frail patients, patients in shock, those with diseases in other organ systems, obesity, and other local factors such as adhesions that hinder the expeditious completion of PCV.

Having elected to do a PCV, how may the duodenum be approached in order to carry out transfixion of the bleeding ulcer? In most cases a duodenotomy, sparing the pyloric ring, grants adequate exposure. However, if exposure is poor, the pylorus can be transected longitudinally and reconstructed in the line of the incision.[2] It is not necessary to resuture the incision as a pyloroplasty. This can be done with impunity since no gastric outlet obstruction ensues as shown by five of Johnston's cases[2] and one of ours. It is stressed, however, that duodenotomy alone supplies sufficient exposure in the vast majority of cases. How should the duodenotomy be closed? In many of our cases we closed the defect transversely, but this seems unnecessary as those we closed longitudinally suffered no ill effects. This is shown in other reports as well.[1,3]

With regard to bleeding gastric ulcer, most surgeons, for fear of leaving behind a gastric cancer, would opt for a gastric resection, without vagotomy, in which the ulcer is included in the specimen. However, most of the arguments stated above concerning patients with bleeding duodenal ulcer apply as well to gastric ulcer, especially that gastric resection has a lower recurrent ulcer rate but at the expense of a higher operative mortality.[14] Some surgeons would prefer the greater immediate safety of a vagotomy provided adequate pre- or intraoperative biopsies have excluded malignancy. As far as choosing PCV over TV, the rationale is similar to that governing duodenal ulcer. The ulcer is approached *via* a gastrotomy, biopsied and transfixed, or preferably excised totally. If a PCV is to be performed, Johnston[2] warns that the gastrotomy should be made close to the greater curvature of the stomach in order to avoid damage to the vagal nerve fibers entering across the lesser curvature, and to obviate leaving an ischemic strip of gastric wall adjacent to the lesser curvature after the PCV has necessitated ligation of vessels supplying the right side of the stomach.

We have found reports of 80 patients in the literature treated for bleeding peptic ulcer by emergency PCV.[1–7] The vast majority of these are duodenal ulcers, but eight cases of gastric ulcer[1–3] and a single prepyloric ulcer[7] are also reported. There is not a single case of postoperative mortality or early rebleeding. Postoperative morbidity is low. Six papers encompassing 66 patients[1–5,7] report recurrent ulceration in six cases (9%) in a follow-up ranging from 1 month to 10 years.

If we pool our patients with those in the literature, out of 103 cases two died and one suffered postoperative rebleeding. This may be compared with a mortality of 20–30% for emergency gastrectomy in unselected cases.[11,12,15] Among the 89 patients in whom statistics of recurrent ulceration are given, the incidence was 9%. These very impressive results must be tempered by two facts: the patients treated in this paper and in most others in the literatuare were highly selected. Those having disadvantageous local or general conditions underwent some other operation. Secondly, the incidence of recurrent ulcer after PCV increases with time[13] so that the papers with short follow-up duration such as ours and others bias the data toward an apparently low recurrence rate. The extremely low incidence of early rebleeding is noteworthy and contrasts starkly with previous reports[11] of a 20% rehemorrhage rate after vagotomy.

From this study and from those previously published, it seems that PCV may be used as an emergency operation for bleeding peptic ulcer in selected cases with a low mortality, rebleeding rate, and incidence of recurrent ulceration.

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Physiologic Assessment of the Four Commonly Performed Endorectal Pullthroughs

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The popularity of the endorectal pullthrough for the treatment of benign mucosal diseases of the rectum has created a controversy regarding the need for a reservoir. The four currently advocated procedures, the straight endorectal anastomosis, the J pouch, the S pouch, and the lateral isoperistaltic ileal reservoir were evaluated in a puppy model with four animals in each experimental group. Measurement of rectal capacitance showed that all groups achieved 80–85% of control values at 6 months after surgery. Intestinal transit time decreased by one-half in all groups. Stool consistency, stool culture, water, and electrolyte absorption did not show any statistical superiority of one group over another. Stool frequency varied widely at 6 months; 10 stools per 8-hour period were counted in the lateral reservoir group *versus* 25 with the J pouches, and 16 with the straight and S groups. Stool frequency did not correlate with transit time, stool consistency, or rectal capacitance. Barium enemas showed that straight pullthroughs more closely resembled the measurements of the normal animal's endorectal canal. Based on these studies, there appears to be no advantage to adding a reservoir to the endorectal pullthrough.

MUCOSAL AND OTHER benign diseases of the colon and rectum, when requiring surgical intervention, were treated previously by complete protocolectomy with permanent ileostomy.[1,2] This procedure, which removes all the diseased tissue in the rectum, has become the standard surgical approach for both benign and malignant diseases of the rectum. The preservation of the normal pathway for defecation and the absence of an abdominal stoma have remained important to patients and surgeons and, thus, the operations designed to preserve the rectal sphincters, while simultaneously removing all existing and potential disease of the mucosa, have emerged.[3-7] The procedure consists of a standard abdominal colectomy, mucosal protectomy, and an endorectal ileoanal anastomosis. This removes all the rectal disease, preserves innervation to the rectum, bladder, and genitalia, and thus retains the usual pathway for defecation. This procedure, referred to as the endorectal pullthrough, has become the treatment of choice for ulcerative colitis, the potentially malignant disease, familial polyposis, and in some centers, for total colonic Hirschprung's disease.[8-14]

Variations of the endorectal pullthrough have emerged. The procedure, as originally described, involves a straight ileoanal anastomosis. Modifications have involved the creation of a pouch from terminal ileum in order to increase reservoir capacity and, thereby, decrease stool frequency. Initially, the Parks' S-shaped reservoir was introduced.[15] After reports of patients requiring intubation of their pouch for adequate evacuation, other procedures were introduced. Utsunomiya and colleagues described the J-shaped ileal reservoir with good results.[16] Finally, Fonkalsrud has described the lateral isoperistaltic pouch, created in two stages.[17] Proponents of the "reservoir"procedures claim that creation of these pouches improves stool frequency and continence, whereas proponents of the straight

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pullthrough feel that the pulled-through ileum will dilate to the appropriate-sized reservoir over time.[18]

Although several large series of patients who have undergone the various endorectal pullthroughs have been reported, no controlled studies have been carried out, making physiological and clinical comparison of these four procedures difficult.[19–21] For this reason, the following controlled animal experiment was performed.

Materials and Methods

Sixteen 4-month-old, conditioned Beagle puppies were used; four animals were randomly assigned to each of the four experimental groups (straight endorectal pullthrough, J pouch, S pouch, and lateral isoperistaltic ileal reservoir). Beagle puppies have been used previously as an animal model for this type of experiment and were used here to facilitate comparison of this work with other studies.[22–26]

Before surgery, the following parameters were assessed in each animal: general health, stool consistency, perineal irritation, soiling, body temperature, hydration status, and body weight (Table 1). In addition, the following studies and analyses were performed: stool frequency, intestinal transit time, stool cultures, platelet count, hemoglobin concentration, hematocrit, white and red blood cell counts, water absorption using deuterium oxide, and electrolyte absorption using sodium bromide. Rectal manometrics and barium enemas were performed on all animals.

Water Absorption Studies

Deuterium oxide has been used previously to assess water absorption from the bowel in mammals.[27,28] A 2.5-mL/kg dose of deuterium oxide was given to each dog *via* an orogastric tube placed into the animal's stomach. Blood samples were drawn for deuterium oxide analysis prior to administration of the deuterium oxide at ½, 1, 2, and 3 hours after deuterium administration.

Following double-vacuum, freeze distillation of the serum to remove solutes and impurities, the serum distillates were analyzed for deuterium oxide concentration by the falling-drop method.[29]

Electrolyte Absorption Studies

Previous investigators have shown that sodium bromide absorption directly parallels the absorption of sodium chloride.[30–33] Sodium bromide concentration was used as a marker of sodium chloride absorption according to the formula described by Wolf and Eadie.[34]

A 4.0-mL/kg dose of 5% sodium bromide was administered *via* an orogastric tube and blood samples were obtained in the same manner as described under the water absorption studies. Serum bromide was analyzed by a spectrophotometric technique modified and refined in our laboratory for the accurate determination of serum bromide levels.[35]

TABLE 1. *Test/Parameter and Frequency Protocol*

Test/Parameter	Frequency
General health	Daily
Stool consistency	Daily
Perianal irritation	Daily
Soiling	Daily
Body temperature	Daily ×1 week, weekly thereafter
Hydration status	Daily
Body weight	Daily
Serum chemistries (bun, albumin, sodium, potassium, chloride, bicarbonate)	Preop, 1 and 2 weeks, 1, 3, and 6 months
Fecal fat analysis	Preop and monthly
Stool cultures	Preop and monthly
Hematology data (platelet count, hemoglobin, hematocrit, white blood cell count, red blood cell count)	Preop, 2 weeks, 1, 3, and 6 months
Water absorption (deuterium oxide)	Preop, 2 weeks, 1, 3, and 6 months
Electrolyte absortion (sodium bromide)	Preop, 2 weeks, 1, 3, and 6 months
Endoscopy of rectum	2 weeks, 1, 3, and 6 months
Biopsy of ileal mucosa	Preop and 6 months
Rectal manometrics (resting sphincter length, rectal capacity at various distances from anus)	Preop, 1, 3, and 6 months
Stool frequency	Preop and monthly
Transit time	Preop and monthly

Intestinal transit time with charcoal, stool frequency per 8 hours, evaluation of stool consistency, quantitative stool cultures, and sigmoidoscopy were carried out before and after surgery.

Manometric Studies

Manometric studies were used to evaluate postoperative continence. Continence, as defined by Gaston, consists of sphincter continence with its neurologic components and reservoir continence.[36] Normal sphincter continence should be present in all of the animals since rectal musculature preservation was achieved in all four endorectal pullthroughs. Reservoir continence is the variable factor and depends on the type of procedure and length of time since surgery.

The animals were given light general anesthesia (rompun and pentobarbitol) and the distal bowel was cleaned using a tap water enema. Studies have shown that anesthesia has no effect on rectal manometric pressure recordings.[28]

Small amounts of lubricant were applied to an Arndorfer rectal manometry probe (Arndorfer Medical Specialties, Inc., Greendale, Wisconsin), which was inserted through the anus and advanced 10 cm into the distal bowel. The probe is a continuous perfusion type with distal side ports and a balloon at the tip with a separate inflation port. The probe is attached to a pump for continuous, consistent perfusion of water and is then attached to a transducer and chart recorder. The studies performed were:

1. *Resting length of the anal sphincter.* The resting length of the anal sphincter was measured by steady withdrawal of the rectal probe using a pump at a continuous speed. Preoperative control values were obtained in each animal and postoperative changes were observed.

2. *Sphincter response to distension of the bowel.* A transient decrease of intraluminal pressure at the level of the proximal part of the anal sphincter should be observed following distension of the rectal wall. This normal rectoinhibitory reflex was observed before surgery and was reassessed after the pullthrough procedure. The probe was inserted into the rectum with the balloon at the distal tip. Increments of air were instilled into the balloon until responses were obtained at distances of 1–10 cm from the anus.

3. *Capacity of distal bowel.* The rectal probe and balloon were inserted in the same manner as previously described. Air was instilled into the ballon until a deflection was observed on the chart recorder. This was estimated to be the minimal tolerable capacity of the rectum, since this same deflection is observed in humans when they communicate an initial sensation of fullness in the rectum. Air was further instilled into the balloon until a second deflection was noted. This correlates with the maximum tolerable volume. These measurements were repeated at 1-cm intervals up to 10 cm from the anal verge. Changes in rectal capacitance after surgery are an important parameter to assess because stool frequency is directly related to rectal capacitance.

Operative Technique

Following the preoperative tests and assessments, each dog was prepared 24 hours prior to surgery with 250 mg of ampicillin and 10 mg of kanamycin, by mouth, four times. On the day of surgery, the animals received a mechanical bowel preparation consisting of a soap water enema followed by a flushing of the rectum with sterile saline until the returns were clear. The animals were then sedated with a subcutaneous injection of 2.5 mg/kg of xylazine, followed by general anesthesia *via* the intravenous administration of 20 mg/kg of sodium pentobarbitol. Immediately before surgery, 10 mg of chloramphenicol was given subcutaneously followed by irrigation of the rectum with a betadine solution. Sterile technique was observed throughout the operative procedure.

A total colectomy was then carried out to the level of the peritoneal reflection of the rectum. The submucosal stripping was then begun at the level of the peritoneal reflection and continued all the way down to the anus from the abdominal approach. Once the dissection was carried down to the anus, the top of the mucosal tube was grasped with a long clamp and everted outside the anal opening. At this point, attention was redirected to the terminal ileum depending on the type of procedure to be carried out. The following types of pullthroughs were performed:

1. *Straight endorectal pullthrough.* The straight endorectal pullthrough[18] was created as described by Coran. The distal ileum was anatomosed directly to the anus. The anastomosis between anorectal mucosa and the full thickness of ileum was with interrupted sutures of 4-0 Vicryl.

2. *J pouch.* The J pouch[16] was created from the terminal ileum and placed in the rectal muscular cuff. A long side-to-side anastomosis was performed using 4-0 silk interrupted sutures. The length of the pouch from anus to the most proximal portion was 5–7 cm, which is consistent with the size of the animal. The top of the rectal cuff was attached loosely to the pouch.

3. *S pouch.* The S or "Parks" pouch[15] was also created from the terminal ileum and then placed inside the rectal muscular cuff in a similar manner to that described for the J pouch. The terminal 20 cm of ileum was folded twice to give three segments of bowel, the proximal two of which were 5–7 cm long with the distal segment 7–9 cm long. The additional length of the terminal portion allowed for a 2-cm segment of ileum to project beyond the pouch for anastomosis. The ileum was opened on its antimesenteric border and the edges were then folded together to complete the pouch. The distal portion was pulled through and anastomosed in a manner identical to that described for the straight endorectal pullthrough. The top of the rectal cuff was attached loosely to the pouch.

4. *Lateral isoperistaltic ileal reservoir.* The lateral side-to-side ileal reservoir[17] is created in a two-stage procedure in the human. A one-stage procedure was used in this experiment with careful adherence to the dimensions and techniques as described by Fonkalsrud.[37] The proximal end of the distal ileum was oversewn with a purse-string suture and the distal end was anastomosed to the free edge of the anal mucosa. The second step of the procedure involved the construction of a side-to-side reservoir, which was performed at the same operation.

No temporary ileostomy was created in any of the animals.

TABLE 2. *Hydration Status, Perineal Irritation, and Stool Consistency*

Time (weeks)	Per Cent of Animals with Clinical Dehydration				Per Cent of Animals with Perineal Irritation				Per Cent of Animals with Normal Stools			
	C*	J†	S‡	L§	C	J	S	L	C	J	S	L
Before surgery	0	0	0	0	0	0	0	0	100	100	100	100
After surgery												
2	100	100	100	75	75	100	75	75	0	0	0	0
4	100	—	50	100	100	100	100	75	100	100	100	25
6	100	100	0	100	100	100	100	75	0	25	0	100
8	0	25	0	25	100	75	100	100	25	100	100	100
10	0	25	0	25	100	100	100	100	100	25	100	100
12	50	0	0	100	75	100	100	100	100	100	100	100
14	0	50	0	75	75	100	50	100	100	100	100	100
16	0	50	0	75	75	100	50	100	100	25	100	100
18	50	25	0	50	75	100	25	75	100	50	100	25
20	50	50	25	0	25	100	25	25	100	100	100	100
22	0	25	0	—	100	100	0	100	100	100	100	0
24	25	0	0	0	100	75	50	100	25	25	100	25

* C = straight pullthrough.
† J = J pouch.
‡ S = S pouch.
§ L = lateral isoperistaltic ileal reservoir.

Postoperative Evaluation

The following postoperative protocol was used. The animals were administered subcutaneous injections of 10 mg of chloramphenicol twice daily for 7 days. In addition, they received a subcutaneous administration of 10 mL/kg/24 hours of sterile normal saline for 7 days after surgery to help prevent dehydration in the immediate postoperative period. Dogs were allowed standard puppy chow and water *ad libitum* throughout the 6-month postoperative period. No special dietary supplements were added and no medication (*e.g.*, Metamucil®, Lomotil®, or immodium) was administered to reduce stool frequency.

The previously described tests and analyses were assessed in each of the experimental animals according to the frequency listed in Table 1. General health, stool consistency, degree of perineal irritation, presence of soiling, hydration status, and body weight were assessed on a daily basis. Body temperature was obtained daily for 1 week after surgery, and weekly thereafter. If fever occurred, appropriate evaluation was carried out and close monitoring was resumed until a normal temperature was reached. Blood chemistries and hematologic analyses were obtained during the postoperative course as clinically indicated. Fecal fat analyses, stool cultures, stool frequency, and intestinal transit time were obtained on a monthly basis. Rectal manometrics were performed at 1, 3, and 6 months after surgery. Water and electrolyte absorption studies were carried out during the second week after surgery, and at 1, 3, and 6 months. Rectal endoscopy was performed at 2 weeks, 1, 3, and 6 months after surgery. The rectal pouch was dissected intact at autopsy for histologic analysis as previously described.

Barium Enema

Barium enemas were performed under fluoroscopic control by a radiologist (E.R.B.). Several nonoperated animals were studied and used as controls. Measurements were taken to assess the following: (1) small bowel diameter at 5 cm above the rectal pouch, (2) anteroposterior diameter of the pouch, (3) measurement of the endorectum caudal to the pouch, and (4) length of the pouch.

Results

Hematocrit, mean corpuscular red cell volume, and platelet count showed no differences between groups. All animals showed an initial but unsustained drop in hematocrit in the early postoperative period, as would be expected since these major operations were undertaken without blood transfusions. All groups developed a leukocytosis (as high as 20,000), which was most marked during the first postoperative week.

Parameters such as weight, appearance, behavior, and posture assumed for defecation were all monitored by observation at frequent intervals. The animals' activity returned to the preoperative level by 1 month after surgery in all groups. The dogs were uniformly mildly dehydrated for approximately 2 months after surgery. Perineal irritation was found in over 50% of animals, even at autopsy. Fifty per cent of S pouches, 75% of J pouches, and 100% of the lateral and straight groups

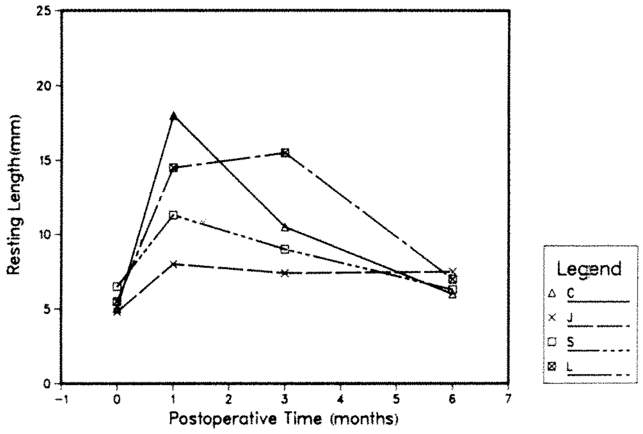

FIG. 1. Changes in mean resting sphincter length over 6-month period.

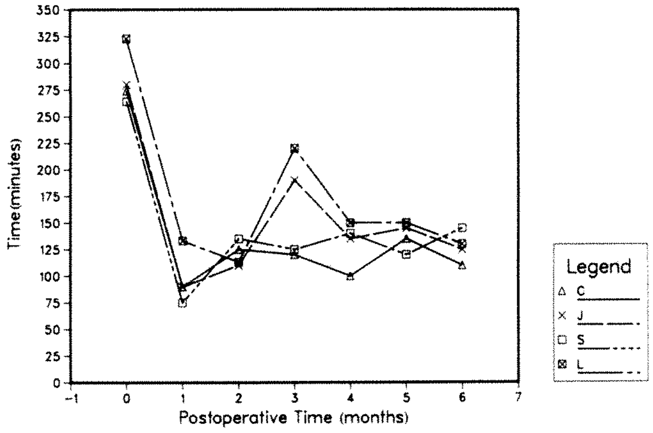

FIG. 3. Changes in mean intestinal transit time over 6-month period.

demonstrated the presence of perineal irritation (Table 2). The straight, S, and lateral reservoir groups were observed to have normal squatting posture while defecating. No animal with a J pouch was observed to have normal posture while defecating; straightening of the body while standing against a wall or lying prone was frequently observed at defecation in these animals. Body weight increased from 2 to 3 kg over the 6-month period in all groups. All animals weighed 6–7 kg at the onset of the experiment and 7 to 9 kg at the 6-month period.

Manometric data are shown in Figures 1 and 2. The resting sphincter length was found to be 5–6 cm in all groups both before and 6 months after surgery. There was a transient increase of two to three times the original length at 5 weeks after surgery, which gradually returned to normal by 6 months in all groups except the J pouches, in whom no significant postoperative changes occurred. Maximum volume or rectal capacitance is expressed as a percentage of control value. The four groups uniformly achieved 80–85% of control at 6 months. The lateral and S pouches decreased to their lowest maximum volume of 50 and 47%, respectively, at 1 month, whereas the lowest maximum volume for the straight group was 75%. The J pouches continued to decrease in volume until 3 months after surgery, when they reached their lowest volume of 50%. The difference between the straight pullthrough dogs and the lateral pouch dogs was statistically significant ($p < 0.05$).

Intestinal transit time in all dogs before surgery was 275–325 minutes (Fig. 3). All groups demonstrated similar patterns of maximum decrease to nearly 75 minutes at 1 month after surgery and a gradual rise to 125–150 minutes at 6 months; this was approximately one-half of the preoperative value. Stool frequency showed greater variation between groups and did not correlate with transit time (Fig. 4). The J pouch dogs experienced 25 stools per 8-hour waking period, the straight and S pouches had 16 stools, and the lateral reservoir animals had 10 stools at the end of the study period. Consistency of stools (Table 2) did not appear to correlate with either frequency or transit time. Only 25% of the J, straight, and lateral pouch dogs achieved a formed stool at the

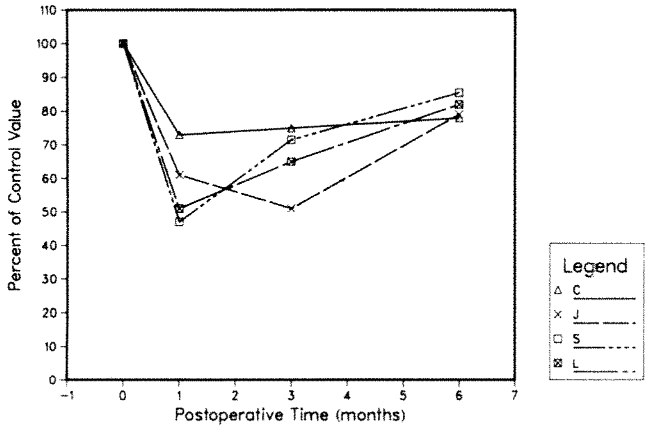

FIG. 2. Changes in mean rectal capacitance over 6-month period.

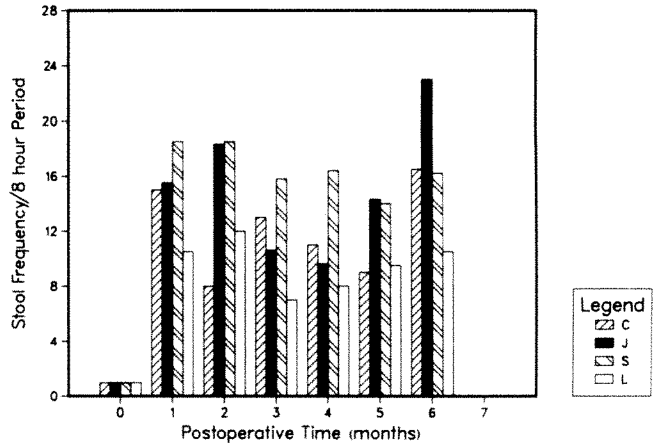

FIG. 4. Changes in mean stool frequency over 6-month period.

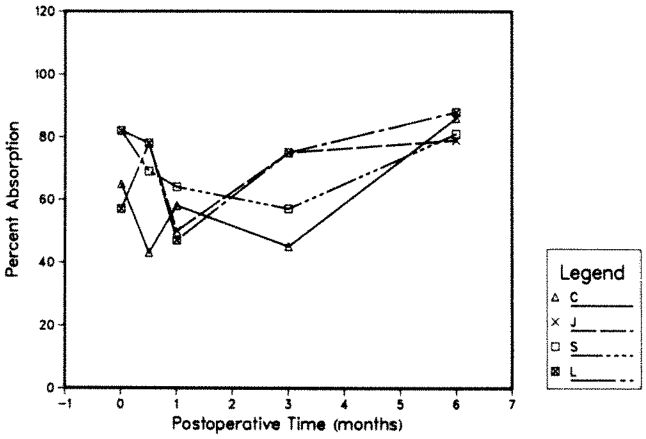

FIG. 5. Changes in mean deuterium oxide (water) absorption over 6-month period.

six-month period, while none of the S pouch dogs produced a formed stool.

Postoperative stool cultures in all groups showed normal canine intestinal flora. Overgrowth of particular organisms or appearance of organisms not usually found in Beagle feces did not occur.

Mean water absorption is depicted in Figure 5. The dogs showed a general decrease in absorption at the 2-week and 1-month time periods, followed by an increase in absorption to preoperative values at the 6-month time period. The final mean water absorption percentages in all the animal groups were 84%, which is the same as the preoperative values. Electrolyte absorption remained unchanged in the straight and S groups. In the J group there was a transient increase at 1 month, followed by a decrease at 3 and 6 months. In the lateral reservoir group there was an increase at the 2-week period that decreased at 1 month, then reversed and continued to increase until the end of the study period (Fig. 6). The final electrolyte absorption percentages at the 6-month period were statistically the same as the preoperative values in all groups, even the lateral reservoir animals.

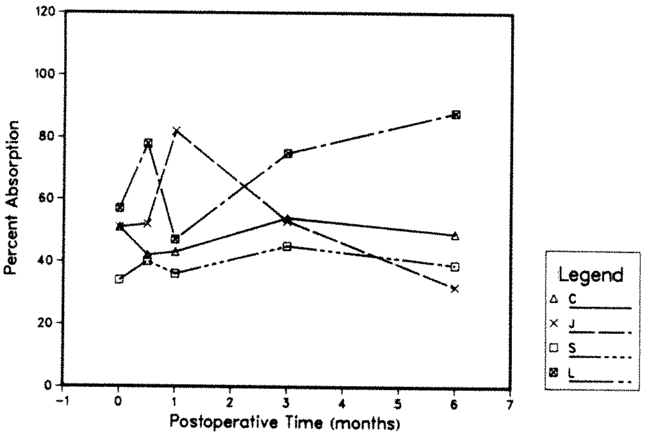

FIG. 6. Changes in mean bromide (electrolyte) absorption over 6-month period.

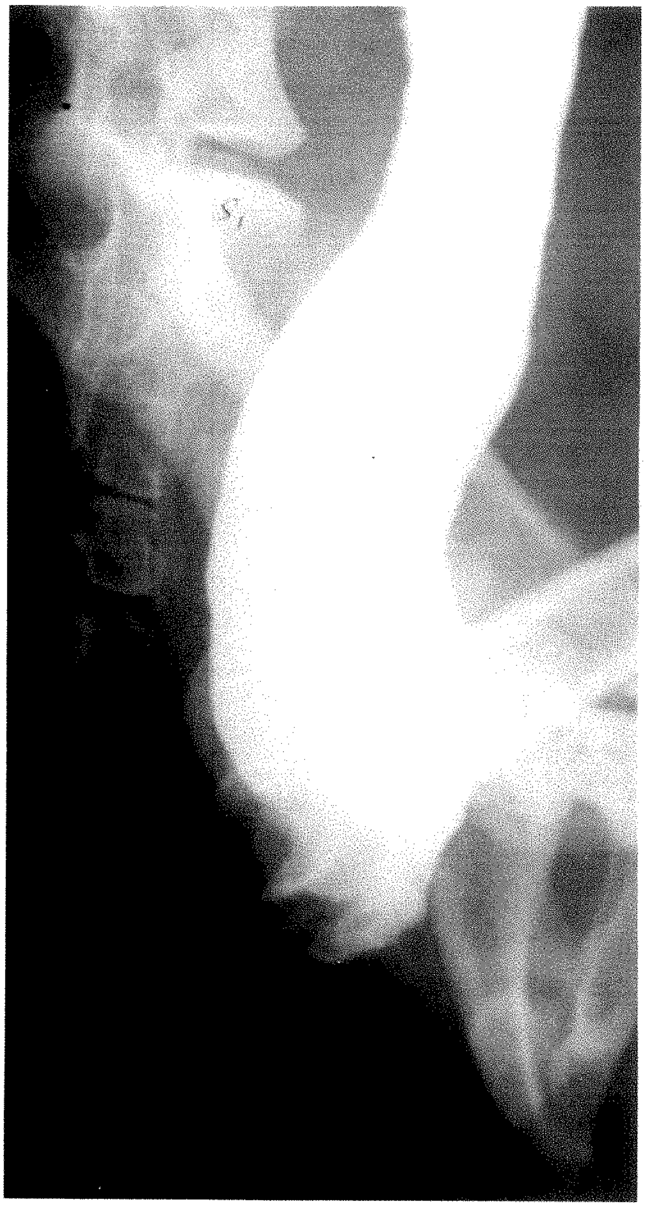

FIG. 7. Barium enema in normal dog.

Barium enemas were obtained 6 months after surgery. The configuration of the straight pullthroughs most closely approximated that of the normal animal's endorectal canal; however, the volume of the straight pullthrough was generally smaller than seen in the other groups (Figs. 7 and 8). One dog with a straight pullthrough developed moderate dilatation of the ileum within the endorectal canal and tapering caudally at the anal canal. The remaining three dogs with a straight pullthrough had only mild dilatation of the neorectum that was comparable to the ileum proximal to the rectal

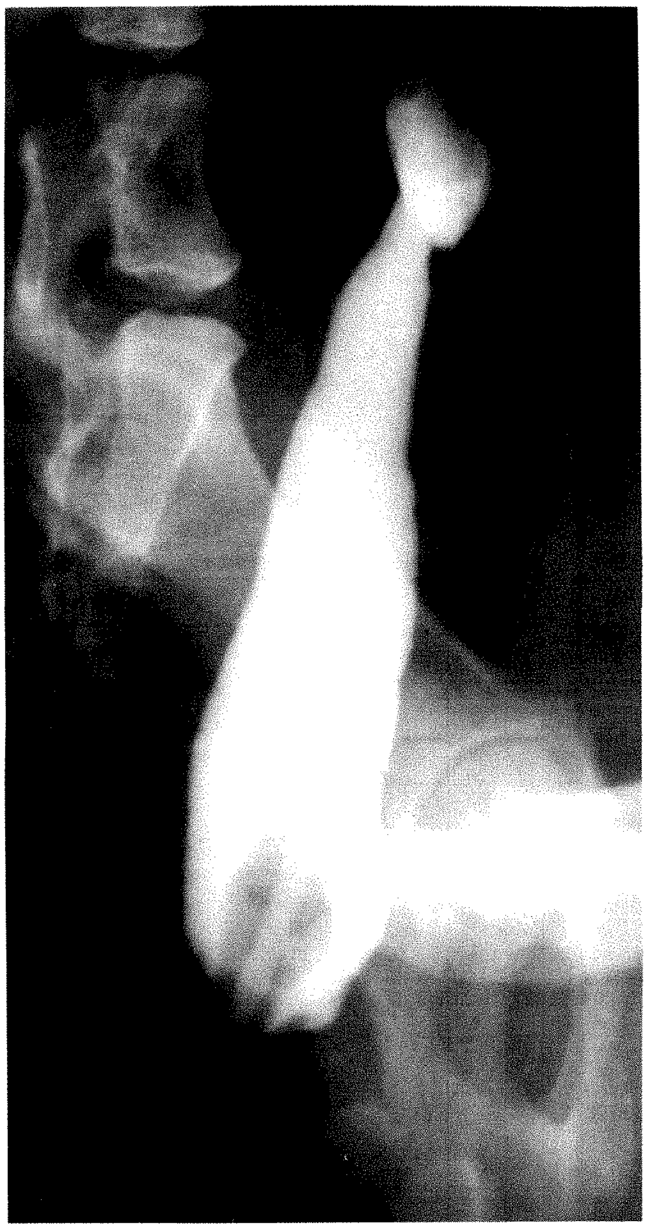

FIG. 8. Barium enema 6 months following endorectal pullthrough with straight ileoanal anastomosis.

cuff. In both the S group (Fig. 9) and the lateral group (Fig. 10), a discrete reservoir was present; however, there was an abrupt transition between the small bowel proximal to the cuff and the small bowel within it. All dogs in the J group (Fig. 11) had an abrupt change in caliber between the small bowel proximal to the cuff and the neorectum; there was a discrete outpouching at the top of the cuff in all of these dogs. The diameter of the small bowel approximately 5 cm above the top of the rectal cuff was greatest in the straight group, suggesting a larger reservoir proximal to the cuff in this group.

Histopathologic evaluation was done for all animals when killed 6 months after pullthrough, except for one in the S pouch and one in the lateral reservoir groups. In each group, the muscularis of the pulled-through segment of ileum was generally bound to the rectal muscular cuff by a thin layer of young scar tissue. Mucosae appeared intact in the region of ileoanorectal anastomosis. The appearance of the terminal ileal (neorectal) mucosa at autopsy was generally not significantly different from that of the ileal sample taken at the time of operation. Minimal mucosal distortion was occasionally evident in the anastomotic region. Microscopic nests of trapped columnar epithelium among the fused muscle layers were evident in only two animals, one in the S pouch group and one in the lateral reservoir group. In the former animal, these nests were situated in an apparent sinus tract, presumably communicating with the bowel lumen in the anastomotic region.

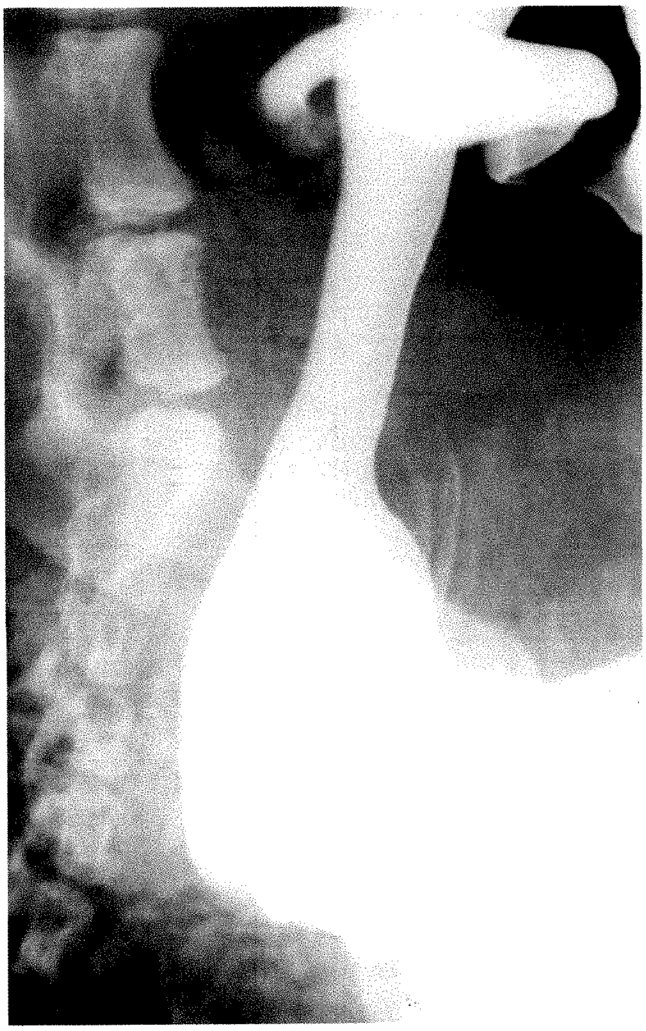

FIG. 9. Barium enema 6 months following endorectal pullthrough with S pouch.

Discussion

The endorectal pullthrough procedures most commonly used in the clinical setting and the procedures evaluated in this investigation are the S pouch, the J pouch, the lateral isoperistaltic ileal reservoir, and the straight pullthrough. The S or Parks' pouch, which was the first reservoir described, is created from three loops of bowel and is placed in the rectal cuff, allowing influence over it by the rectal sphincters, which theoretically facilitate emptying. The disadvantage of the S pouch is the dilatation of the reservoir with subsequent stasis and the related serious problem of pouch inflammation (pouchitis). The theoretical advantage of the lateral ileal reservoir pouch is normal evacuation because both loops are isoperistaltic. However, a portion of the lateral reservoir lies above the rectal cuff; thus, emptying is not totally influenced directly by the rectal sphincters. The J pouch is similar but somewhat smaller than the S pouch and does not dilate as much; however, although reservoir capacity is less, it increases gradually over time. The straight pullthrough has the advantage of greater technical ease of performance than with the reservoir techniques but has the disadvantage of a smaller rectal capacity initially. This rectal capacity increases over time. In this study, the time required to achieve adequate reservoir capacity in the straight pullthrough was longer than in the surgically created pouches. In addition, stasis does not occur in the straight neorectum, so pouch inflammation is not a problem.

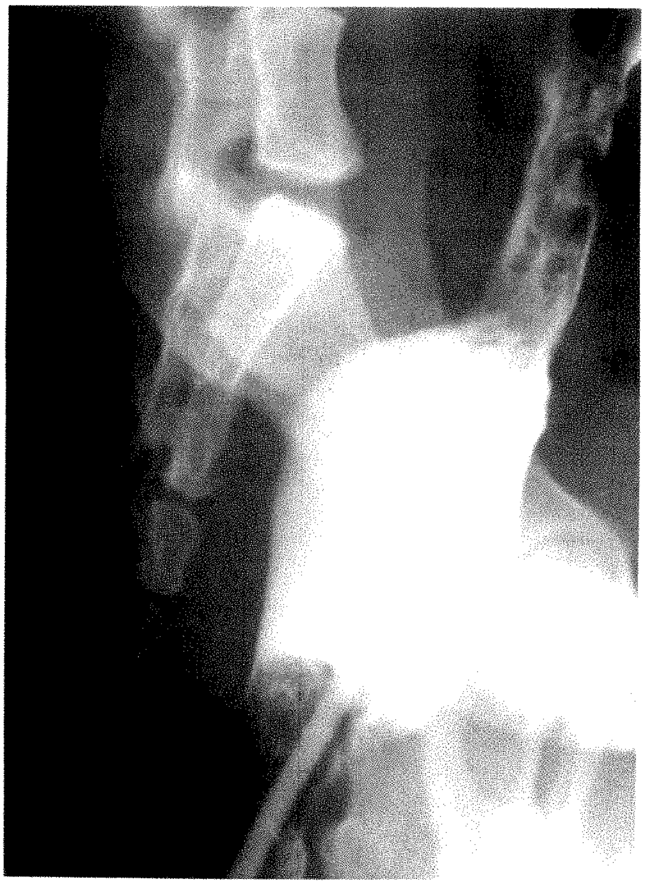

FIG. 10. Barium enema 6 months following endorectal pullthrough with lateral ileal reservoir.

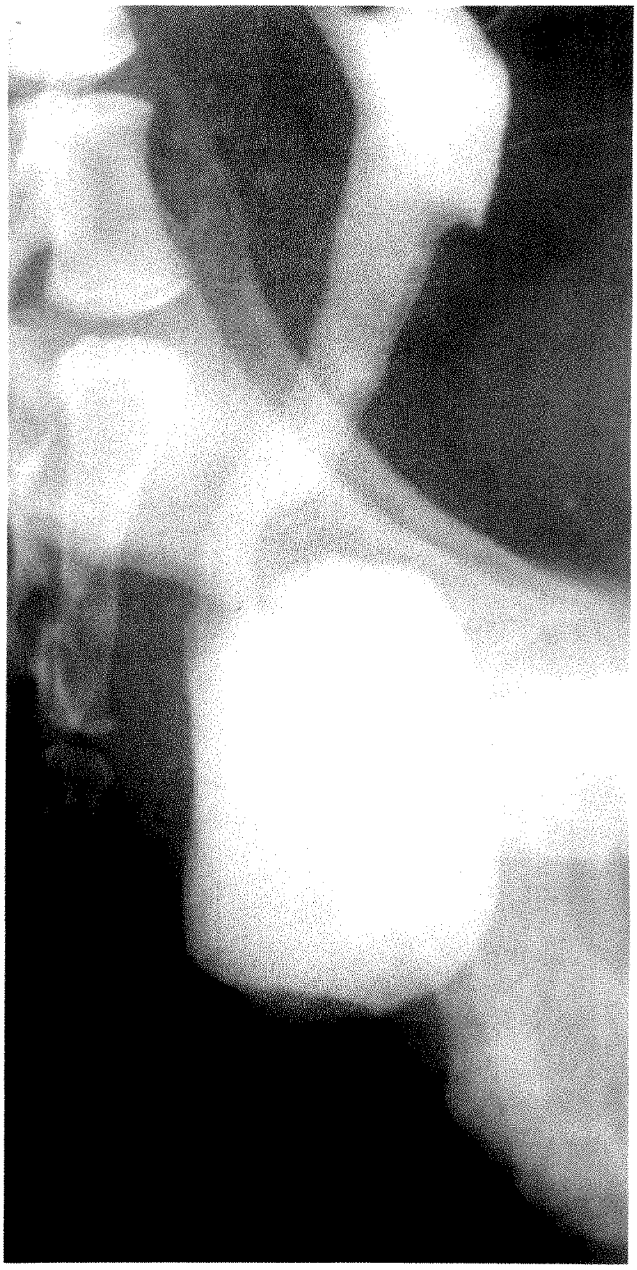

FIG. 11. Barium enema 6 months following endorectal pullthrough with J pouch.

Proponents of the reservoir procedure feel that this approach more closely mimics the normal situation.[15-17] The reservoir function of the rectum is one of the important factors responsible for normal continence. The accumulation of feces in the pouch before expulsion allows for better water absorption, which results in a more formed stool and, thereby, in a decrease in stool frequency. The decreased loss of water and electrolytes in the feces also obviously reduces the risk of dehydration. However, the water and electrolyte absorption data in this study showed no differences between any of the groups and a return to preoperative levels at 6 months. In addition, none of the clinical parameters such as stool consistency or stool frequency were improved by the creation of a reservoir; nor did physiologic parameters such as reservoir capacity improve by the presence of a pouch. In fact, reservoir capacity was greatest in the straight group. Therefore, there appears to be no clinical or physiologic advantage to adding a reservoir to the endorectal pullthrough.

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Experience with the Straight Endorectal Pullthrough for the Management of Ulcerative Colitis and Familial Polyposis in Children and Adults

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The first significant experience with the straight endorectal pullthrough for the management of ulcerative colitis was presented before the American Surgical Association in 1977 by Lester Martin. Since then the operation with or without modification has been used extensively. High stool frequencies in some series led to disenchantment with the straight anastomosis and to the development of various reservoir procedures to increase rectal capacity and thereby reduce frequency. As a result, no large series of straight pullthroughs is available for comparison with the reservoir modifications. Between September 1977 and September 1986, 72 children and adults, 61 with ulcerative colitis and 11 with familial polyposis, underwent endorectal pullthrough (ERPT) and straight ileoanal anastomosis under the overall direction of a single surgeon (AGC). Sixty patients have undergone ileostomy closure and form the basis of this study. Mean age at operation was 22.7 years (range 4–48 yr), and duration of active disease averaged 6 years. One-half of the patients underwent total abdominal colectomy with ERPT as a primary procedure. There were 11 cases of adhesive bowel obstruction following ERPT, and in six patients in the series permanent revision to a Brooke ileostomy was required. One patient died of hepatic failure in the late postoperative period. Follow-up has ranged from 3 months to 9 years. Mean stool frequency for the group as a whole at 3, 6, 12, 24, and 36 months was 11.8, 11.2, 9.6, 9.0, and 8.3 per 24 hours, respectively. Daytime continence was achieved in all patients. Occasional nocturnal soiling occurred in 11.1% of patients at 1 year. Stool frquency and continence were also analyzed by age group above and below 18 years and above and below 30 years. There were no statistically significant differences between these groups. The authors conclude from this study that ERPT with straight ileoanal anastomosis remains an appropriate alternative for children and adults with ulcerative colitis or familial polyposis and compares favorably with the more complicated ERPT involving a reservoir.

NEARLY A DECADE has passed since Lester Martin presented the first large series of endorectal pullthroughs (ERPT) with straight ileoanal anastomosis (IAA) for benign disease of the colorectum before the American Surgical Association in 1977.[1] High stool frequencies prompted researchers into the reservoir capacity and peristaltic abnormalities of the neorectum and led surgeons to develop a variety of reservoir "pouches" to increased rectal volume and thereby decrease frequency.[2-10] The impetus for this approach stemmed from Kock's attempts to create a continent ileostomy.[11] The physiology and relative merits of the various pouch configurations have been extensively reviewed.[12]

Initially conceived by Ravitch and Sabiston,[13] it has now been well established that ERPT with some form of ileoanal or ileopouch-anal anastomosis is the preferred alternative to standard Brooke ileostomy for patients requiring total colectomy for ulcerative colitis and familial polyposis. Most large series report a high degree of patient satisfaction regardless of the type of ERPT.

Promising early experience with ERPT and straight ileoanal anastomosis at the University of Michigan Medical Center[14-19] led us to pursue this approach as the primary alternative to abdominal wall ileostomy in patients requiring total colectomy for ulcerative colitis and familial polyposis. This report reviews our experience with this procedure in chidlren and adults over the past 9 years.

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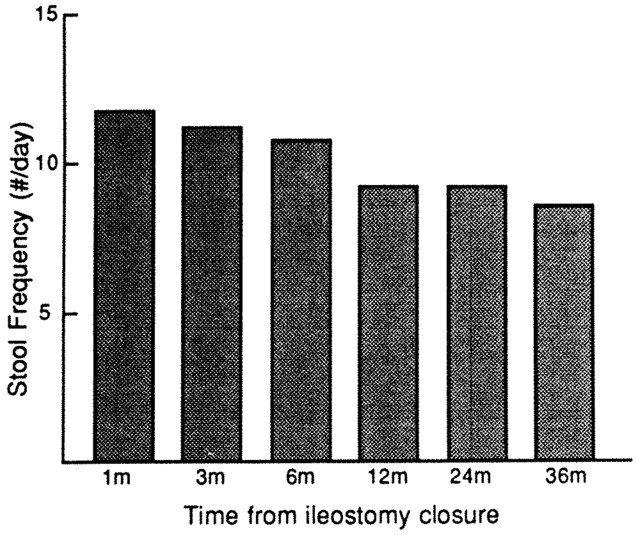

FIG. 1. There is a steady decline in stool frequency following ileostomy closure.

Materials and Methods

Between September 1977 and September 1986, 72 children and adults (61 with ulcerative colitis and 11 with familial polyposis) underwent endorectal pullthrough (ERPT) with straight ileoanal anastomosis under the overall direction of one surgeon (AGC). Sixty patients have undergone ileostomy closure and form the basis of this study. Mean age at operation was 22.7 years (range 4–48 yrs), and duration of active disease averaged 6 years. One-half of the patients underwent total abdominal colectomy and ERPT with temporary diverting loop ileostomy as a primary procedure.

All patients underwent preoperative contrast radiologic studies and sigmoidoscopic or colonoscopic examination with histologic confirmation of the diagnosis.

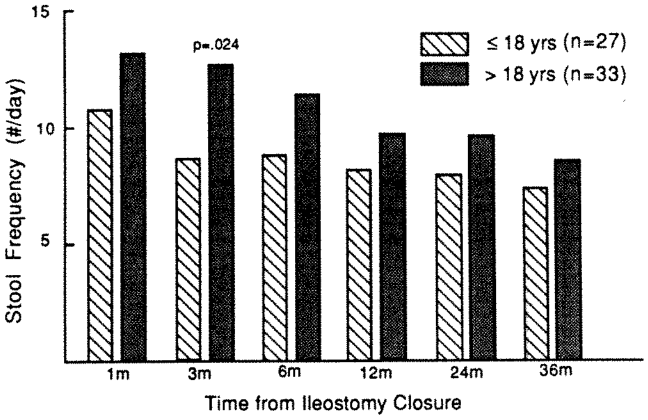

FIG. 2. No significant difference in stool frequency existed between those patients older than and younger than 18 years of age, except at the 3-month follow-up interval.

Standard bowel preparation prior to surgery included a clear liquid diet for 48 hours, oral erythromycin and neomycin the day before surgery, and intravenous ampicillin and gentamicin at midnight and on call to the operating room. Parenteral antibiotics were continued until the fifth postoperative day.

The technique of operation has been described in detail in previous reports.[15,16] To summarize, mucosal proctectomy is begun just below the peritoneal reflection of the rectum. A 4–5 cm muscular rectal cuff is developed. Ileoanal anastomosis is performed using absorbable polyglycolic acid sutures. A closed system drainage catheter is left posteriorly between the muscular cuff and the distal ileum for 24–48 hours. All but six patients underwent a diverting loop ileostomy. Ileostomy closure was performed at an interval of 3–6 months following ERPT.

Follow-up was complete in all patients and involved monthly visits until 6 months after ileostomy closure. The patients were seen every 3 months for 1 year and then yearly. Sigmoidoscopy with or without biopsy of the anastomosis was carried out at each yearly visit to detect any dysplastic changes in the cases of ulcerative colitis and any evidence of new polyp formation or malignant degeneration in the cases of familial polyposis.

The charts of all patients were reviewed for operative details, complications, and postoperative functional results. Patients who had not been seen for 1 year were sent a detailed questionnaire. Stool frequencies were compared at intervals and between age groups using the paired Student's t-test.

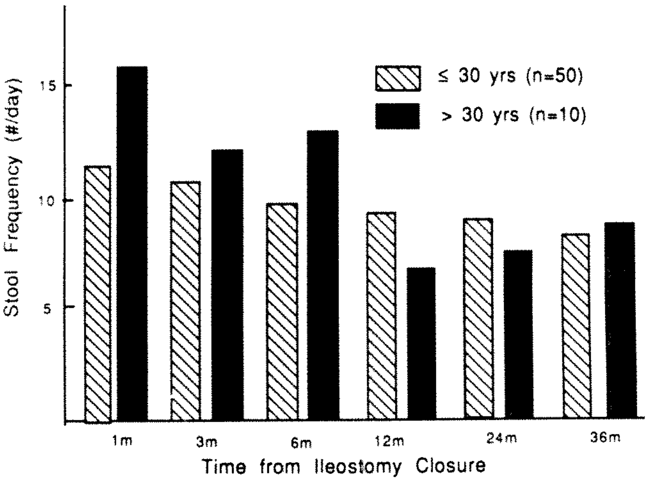

FIG. 3. No significant differences existed in stool frequency between those patients older than or younger than 30 years of age.

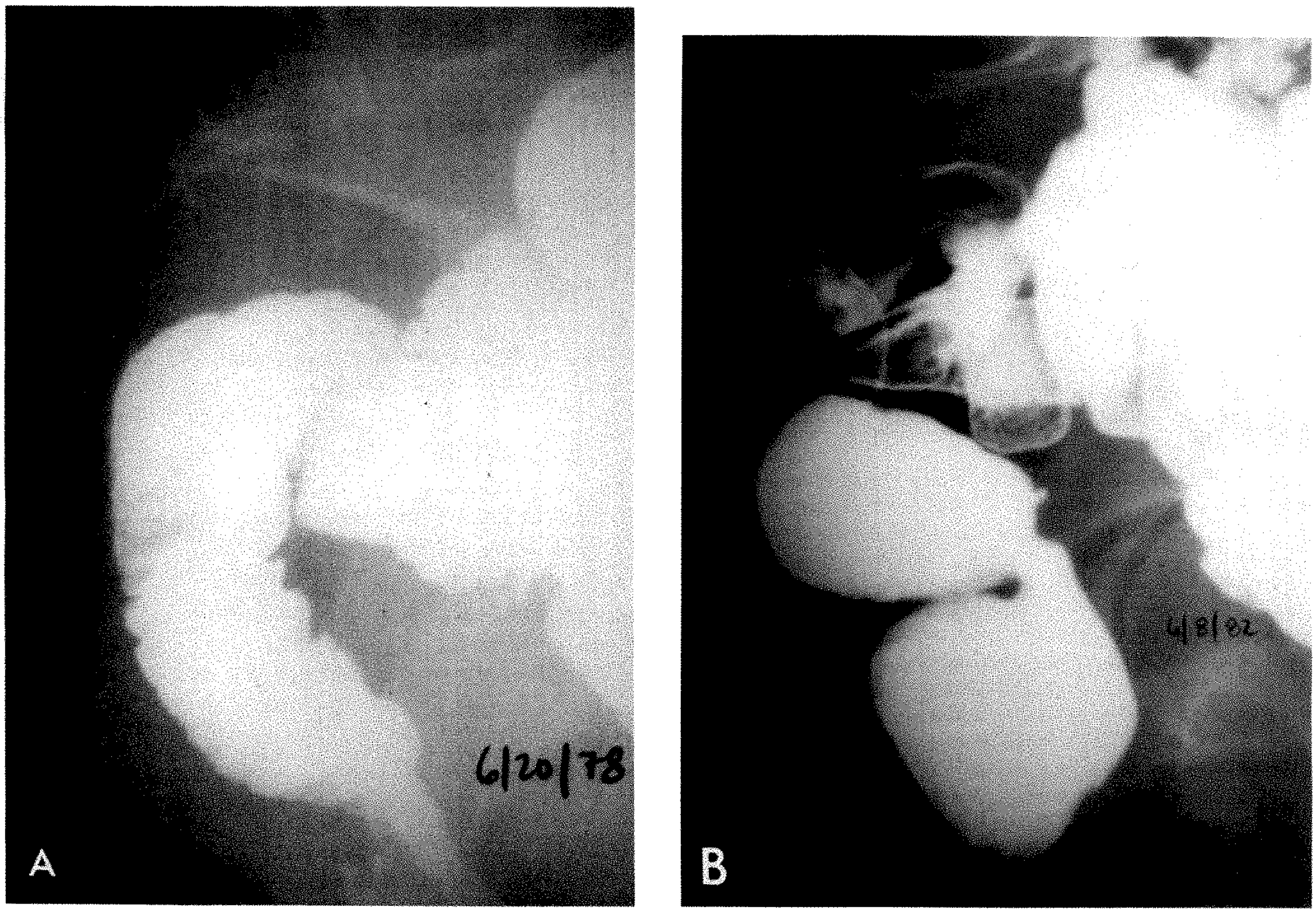

FIG. 4A and B. *A*. Radiographic appearance of the neorectum 2 months following ERPT and straight IAA, just before ileostomy closure. The endorectal canal appears normal but slightly decreased in size. *B*. Appearance of the neorectum 4 years later. The endorectal canal has dilated significantly and appears normal.

Results

Follow-up has ranged from 3 months to 9 years, with an average of 12 months. Overall operative mortality was 1.5% representing a single death that occurred in a steroid-dependent patient who developed small bowel obstruction, sepsis, and ultimately fulminant hepatic failure 8 months after surgery. There were 11 cases of adhesive bowel obstruction following ERPT, six of which required an enterolysis. Pelvic abscess occurred in two patients (3.3%) and required operative drainage. A third patient with a pelvic phlegmon was treated conservatively, with resolution of the infectious process on intravenous antibiotics. Two women developed rectovaginal fistulas, which healed with temporary diversion. Minor wound infections occurred in two patients.

There were no anastomotic leaks. In five patients the ileoanal anastomosis was felt to be narrowed on early digital rectal examination. None of these patients were symptomatic and on later follow-up the anastomoses were felt to be normal.

Six patients (10%) were revised to a standard Brooke ileostomy. One additional patient with familial polyposis was found to have anaplastic carcinoma at the anal margin on histologic examination of the mucosal proctectomy specimen and required abdominal perineal resection. One of the six patients, a 10-year-old girl, who developed recurrent inflammatory bowel symptoms was subsequently found to have Crohn's disease in spite of the fact that a second review of her colon pathology after her ERPT again suggested the diagnosis of ulcerative colitis. Small bowel biopsy many months after ERPT was typical of Crohn's disease even though histologic evaluation of the terminal ileum at the time of ERPT was normal. Two other patients were diverted as treatment for rectovaginal fistula. Only three patients (5%) were reviewed because of dissatisfaction with stool frequency.

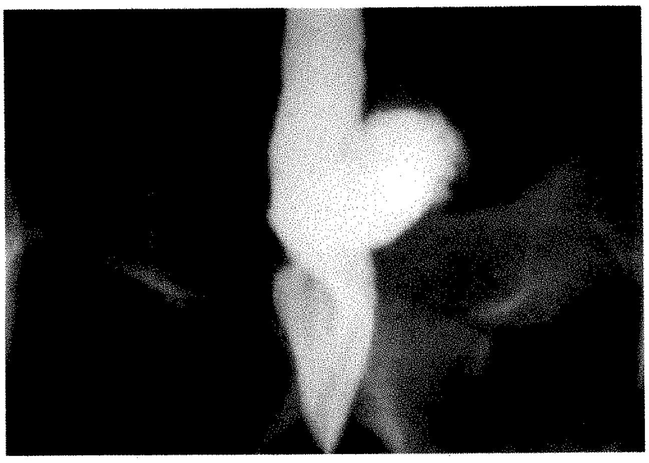

FIG. 5. The endorectal canal appears normal 2 years following ERPT and straight IAA.

Daytime continence was achieved in all but two patients at 3 months, and this reached 100% at 1 year. No patient has had major soiling difficulties. Occasional nocturnal leakage was reported in 11.1% of patients at 1 year.

Mean stool frequency for the group as a whole declined progressively over time to approximately 8 semiformed stools per 24-hour period at 3 years (Fig. 1). All patients were able to evacuate spontaneously.

Stool frequency was also analyzed by age groups above and below 18 and above and below 30 years. There were no statistically significant differences between these groups (Figs. 2 and 3).

Discussion

A recent review of the literature on the endorectal pullthrough suggests that while the addition of a reservoir has led to decreased frequency of bowel movements, it has also created some new problems.[12] These vary from a slightly higher incidence of pelvic abscess to stasis, pouchitis, and inability to evacuate the pouch spontaneously.

Rates of pelvic sepsis in the range of 20% are routinely reported in patients undergoing J or S reservoir procedures.[8,9,20] This is likely due to local disruptions of long suture lines. Even with abscess drainage, pelvic inflammation and scarring has led to anastomotic strictures and the need for revision in some patients.[12] In the current series, pelvic abscess occurred in only two patients (3.3%).

With the development of larger capacity reservoirs, stasis and pouchitis have become an increasing problem. Many series report a 25% incidence of clinically significant pouchitis, often requiring suppressive antibiotic therapy. Of perhaps more concern is the 64% incidence of chronic microscopic inflammation reported by Nicholls in the recent update of the St. Mark's experience with the S reservoir.[20] This is in contrast to our series, in which routine biopsies of the ileum at the ileoanal anastomosis, which are done on a yearly basis routinely, have shown no significant inflammation. Careful follow-up of these patients seems warranted to rule out late development of dysplastic changes, as anectodal cases of carcinoma in the neorectum have been reported.[21]

Finally, spontaneous evacuation has become a problem in at least one large series of S reservoirs.[20] In that report, 53% of the patients were unable to spontaneously evacuate the reservoir and required catheterization for drainage.

Adhesive small bowel obstruction has continued to be a significant source of postoperative morbidity. In the current series, 11 of 72 patients (15.3%) developed bowel obstruction requiring enterolysis after ERPT. This is comparable to the frequency in other reports.[8,9,12]

The variety of ERPT procedures currently in vogue is evidence of the absence of an ideal operation. As discussed, the trend toward highly continent reservoirs is not without problems. Although stool frequencies on the average are somewhat higher with the straight ERPT than with the reservoir modifications, these differences tend to disappear 1–2 years after the procedure. This is further substantiated by our observation that the neorectum created by the straight IAA progressively dilates during the 1- to 2-year period following ERPT and finally attains a normal appearance on barium enema (Figs. 4 and 5).[22] Our current experience suggests that ERPT with straight anastomosis offers the advantages of a shorter operation, complete spontaneous evacuation, absence of pouchitis, and a lower incidence of pelvic sepsis.

We conclude from this study that ERPT with straight ileoanal anastomosis remains an appropriate alternative for children and adults with ulcerative colitis or familial polyposis and compares favorably with the more complicated ERPT incorporating a reservoir.

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Coloanal Anastomosis in the Management of Benign and Malignant Rectal Disease

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The aim was to determine the efficacy, safety, and long-term clinical and functional results of coloanal anastomosis in patients with complicated benign and malignant rectal disease. Twenty-nine patients underwent coloanal or colopouch-anal anastomosis for either carcinoma of the rectum not technically amenable to conventional low anterior resection, severe radiation injury, large benign lower third tumors, or complications of previous operations. The mean age of the patients was 61 years and 82% were men. A diverting colostomy was constructed in 55% of the patients. The mean (±SEM) length of follow-up was 20 ± 3 months. There was no operative mortality. Transient urinary retention, however, occurred in 40%, anastomotic stricture in 28%, and anastomotic leakage in 3.4%. Four patients (14%) could not have intestinal continuity restored and therefore were considered failures. The stool frequency for all remaining patients (N = 25) was 3 ± 1 per day (mean ± SEM) and did not vary with age, sex, or indication for operation. Complete continence was achieved by 84% of patients, but no patient was incapacitated by poor bowel function. In patients in whom a conventional colorectostomy is impractical or unwise, coloanal anastomosis is a safe and efficacious alternative operation that preserves anal continence.

OPERATIONS DESIGNED to preserve the anal sphincter have evolved slowly since Kraske described excision of the rectum and anastomosis of the sigmoid colon to the external sphincters and perianal skin in 1875.[1] In 1885, Kocher reported a transsacral approach that facilitated resection and primary anastomosis for neoplastic growths low in the rectum.[2] In the early 1900s, however, the excellent results obtained by Miles with combined abdominoperineal resection for rectal cancer dampened interest in operations that preserved the sphincters.[3]

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In subsequent decades, better understanding of the direction of lymphatic spread of rectal cancer[4] moderated the view of radical resection held by Miles, thereby renewing interest in sphincter preservation. Dixon advocated anterior resection in the 1940s,[5] but it was not until the reports of Mayo et al.[6] and Wilson and Beahrs[7] that the operation achieved widespread popularity. It is now widely accepted that anterior resection is the procedure of choice in the surgical management of cancers in the middle and upper thirds of the rectum.

For tumors not amenable to low anterior resection for technical reasons, abdominal transsacral resection, abdominal transsphincteric resection, and abdominal anal pullthrough operations have been proposed as alternatives to abdominoperineal resection.[3,8,9] These procedures, however, never became popular, principally because the operations were difficult to perform and complications difficult to manage (such as posterior fistulae). Moreover, predictable functional results were rarely achieved.[10,11] However, coloanal anastomosis (that is, abdominal resection, endorectal mucosal dissection, and direct anal anastomosis, as described by Parks[12]) holds promise; the technique is essentially Soave's.[13] Early reports of bowel function following surgery were good. Recently, this technique has been reported to be useful in patients with benign and malignant rectal tumors and in patients with radiation injury.[14-16] The aim of this study was to determine the safety, efficacy, and long-term clinical and functional results of coloanal anastomosis in the management of benign and malignant rectal disease.

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Materials and Methods

From January 1979 to August 1986, the records of all patients undergoing coloanal anastomosis at the Mayo Clinic were reviewed. Age, sex, indication for operation, type of operation, length of hospital stay, and morbidity and mortality were recorded for each patient. Functional results (in terms of the number of stools per day), the presence of fecal incontinence, and the need for motility altering agents were likewise evaluated. Follow-up was conducted by telephone and/or questionnaire.

Surgical Technique

The rectum is mobilized to the coccyx posteriorly, to the levators laterally, and to the distal prostate or vagina anteriorly. If the operation is for cancer, the rectum is oversewn or stapled below the tumor. Endorectal mucosal resection is then performed *via* the *perineal* approach in a manner similar to that described for ileoanal anastomosis.[17] The specimen is removed. The end of the colon is then brought through the resulting muscular cuff of the rectum and anastomosed to the mid anal canal. Alternatively, a preanastomotic J-shaped colon reservoir can be constructed by hand or with the stapler, and the apex of the pouch anastomosed to the anal canal (Fig. 1). The left colon and splenic flexure should be mobilized in their entirety in order to ensure that the colon reaches the anus without tension. The pelvis is drained by two suction catheters placed behind the neorectum from above. A diverting loop ileostomy or colostomy should be constructed in most patients.

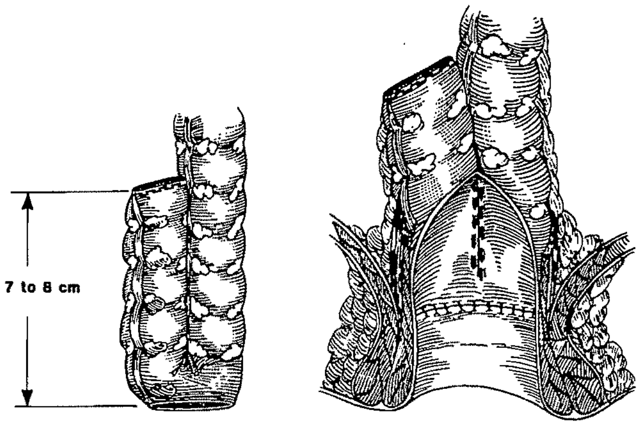

FIG. 1. Diagram of a colopouch-anal anastomosis. The pouch has been constructed with the stapler, incorporating 7–8 cm limbs. The anastomosis to the anal canal is hand sewn. The rectal muscle cuff is short (4 cm).

Results

Thirty-nine patients have undergone coloanal anastomosis and 29 have been followed for a minimum of 3 months, forming the basis for this report. There were 24 men (82%) and five women (17%). The mean age at the time of operation was 61 years (range: 45–75). Indications for operation included carcinoma of the rectum (19 patients), radiation injury (5 patients), villous adenoma (3 patients), and complications of prior surgical procedures (2 patients). Three patients had a *preanastomotic reservoir* constructed. All coloanal anastomoses were handsewn. Sixteen (55%) of the patients had a protective colostomy constructed that was closed a mean of 12 weeks after coloanal anastomosis. The mean (±SEM) length of hospitalization was 14 ± 1 days after the coloanal procedure and 9 ± 1 days after closure of the colostomy. Follow-up was complete in 28 of 29 patients; the mean (±SEM) length of follow-up was 20 ± 3 months (range: 3–54 months).

Mortality and Morbidity (Table 1)

There was no operative mortality. Transient urinary retention occurred in 10 patients (40%) and one patient has required continuous self-catheterization. Eight patients (28%) had an anastomotic stricture that required

TABLE 1. *Mortality and Morbidity*

			Morbidity					
		Mortality	Urinary Retention		Anastomotic Stricture		Anastomotic Leak	
Diseases Treated	N	(30-Day)	N	(%)	N	(%)	N	(%)
Cancer	19	0	9*	(47)	6	(31)	1	(5)
Radiation injury	5	0	1	(20)	0	(0)	0	(0)
Benign adenoma and failed LAR†	5	0	0	(0)	2	(40)	0	(0)
Total	29	0	10	(40)	8	(27)	1	(3.4)

* One patient has permanent urinary retention requiring intermittent catheterization.

† LAR = low anterior resection.

TABLE 2. *Tumor Stage* Versus *Histologically Determined Distal Margin and Proctoscopically Determined Location of the Tumor in the Rectum*

Dukes Stage (Astler-Coller)	Distal Margin Mean (cm)	Distance from Anal Verge Mean (cm)
A	5.0	5
B_1	3.5	10
B_2	2.6	7
C_1	1.5	7
C_2	3.3	8

TABLE 4. *Functional Results of Coloanal Anastomosis by Indication for Operation*

Indication	N	Stools/24 hours (Mean)*	Incontinent
Malignancy	19	2.6	1
Radiation injury	5	2.3	1
Benign adenoma and failed LAR†	5	3.5	1

* Differences between groups; $p > 0.05$.

† LAR = low anterior resection.

intermittent dilatation. One patient developed an anastomotic dehiscence for an overall leak rate of 3.4%.

Four patients (14%) underwent reoperation. One developed a mesenteric hematoma causing obstruction of the colon while another developed an anastomotic leak and required diversion. A third patient developed a severe stricture necessitating diversion and the last patient required re-exploration after anal dilatation performed elsewhere perforated the pulled-through colon segment.

Four of the 29 patients (14%) had complications that prohibited re-establishment of intestinal continuity and were considered failures. Postoperative radiation therapy caused a severe stricture in one patient that necessitated permanent diversion. One patient returned for colostomy closure but, because bilateral hepatic metastases were discovered, continuity was not restored. The third patient required a diverting colostomy for recurrent pelvic tumor and the last patient remained diverted because of a nonhealing anastomotic sinus.

Results in patients with rectal cancer. Eighteen patients underwent coloanal anastomosis for adenocarcinoma of the rectum and one for hemangiopericytoma. The distribution of the adenocarcinomas by Dukes classification (Asler-Coller modification) was: Dukes A, one patient (5%); Dukes B_1, four patients (22%); Dukes B_2, four patients (22%); Dukes C_1, one patient (3.4%); and Dukes C_2, eight patients (44%). The mean (±SEM) distance of the tumors *above the anal verge,* by proctoscopic examination, was 8 ± 1 cm. The mean distal clearance was 4 cm (range: 1.5–5 cm) (Table 2). Eight patients (44%) had postoperative radiation therapy.

TABLE 3. *Survival and Recurrence After Coloanal Anastomosis for Adenocarcinoma of the Rectum**

Dukes Stage (Astler-Coller)			Dead of Disease		Recurrence	
	N	(%)	N	(%)	N	(%)
A	1	(5)	0	(0)	0	(0)
B_1	4	(22)	0	(0)	0	(0)
B_2	4	(22)	0	(0)	1	(25)
C_1	1	(5)	0	(0)	0	(0)
C_2	8	(44)	2	(25)	4	(50)
Overall	18	(100)	2/18	11%	5/18	27%

* Follow-up, 20 ± 3 months (mean ± SEM).

Urinary retention occurred in 9/19 patients (47%) but has persisted in only one. Stricturing at the anastomosis was a recurring problem in 6 of 19 patients (31%), and one patient experienced an anastomotic leak. Four patients, as previously noted, were unable to undergo re-establishment of intestinal continuity. The mean length of follow-up of the patients with cancer was the same as for the entire study group. Five patients experienced recurrence of the tumor, four had distant recurrence only, and one had both local and distant disease (Table 3). Two patients with Dukes C lesions (11%) had died of metastatic liver disease at the time of follow-up.

Results in patients with radiation injury (Table 1). There were five patients in this group. Three patients had an anterior rectal ulcer and a concomitant rectal-urethral fistula, one a strictured rectal lumen, and one a transfusion-dependent proctitis. Urinary retention occurred in one patient (20%) and none experienced an anastomotic stricture or leak.

Results in patients with benign disease (Table 1). Three of the five patients in this group had large, nearly circumferential villous adenomas and two had complications of previous low anterior resection. Urinary retention did not occur, but two of five patients (40%) experienced anastomotic strictures.

Functional Results

The mean (±SEM) stool frequency for *all patients* was 3 ± 1/24 hours and did not vary with the indication for operation; the mean number of stools/24 hours was 2.6 in the cancer patients, 2.3 in the irradiated patients, and 3.5 in the patients operated on for benign disease (Table

4). Moreover, stool frequency was not influenced by the age or sex of the patients. Stool frequency decreased during the first postoperative year with most patients relying on stool bulking agents and antidiarrheal medications to maintain their stooling patterns. Of the patients with a functioning coloanal anastomosis (N = 25), fecal continence was achieved by 84% and 61% of patients had three stools or less per day. Three patients were intermittently incontinent and wore protective pads. Importantly, no patient was incapacitated by poor bowel function or required a permanent diverting colostomy for this reason.

Discussion

The proper role of coloanal anastomosis has not been defined. Experience with the procedure has been scant, principally because of the widespread use of circular staplers; at our institution, the coloanal procedure accounted for less than 2% of the sphincter-saving operations performed during the study period. We have documented, however, that coloanal anastomosis and, more recently, colopouch-anal anastomosis can be performed safely, is efficacious, and can restore enteric continence in selected patients with benign or malignant rectal disease.

The use of coloanal anastomosis has been reported previously in the management of complicated radiation injuries of the rectum and for large villous tumors.[14,15,18] We have also found the coloanal procedure helpful in the management of two patients who had complications from prior low anterior resection; its use in a patient with a severe anastomotic stricture and in a patient with an anastomotic leak requiring fecal diversion restored intestinal continuity successfully in otherwise difficult situations. In the management of adenocarcinoma, coloanal anastomosis has traditionally been restricted to those patients in whom it was technically difficult to safely perform an end-to-end anastomosis very low in the pelvis, but in whom acceptable margins of resection could be obtained by anterior mobilization.

Our experience supports the finding of others[14-16,19] that coloanal anastomosis can be performed safely. There were no operative deaths in this series. Morbidity related to pelvic sepsis and anastomotic breakdown, potentially the most serious complications, occurred in only one patient, but a protective colostomy had not been constructed. Only one-half of the patients in this series were diverted at the time of the original operation and, although not mandatory, temporary colostomy or ileostomy would seem prudent.

Problems with transient urinary retention in 34% of patients and anastomotic stricture in 27% were the most common major complications. Ninety per cent of the patients with urinary difficulties were in the group resected for cancer; the etiology of the urinary retention, therefore, was likely related more to the extent of the pelvic resection required in patients with such cancers of the rectum[20] than to the coloanal anastomosis procedure itself. All but one patient regained normal bladder function.

Anastomotic stricture, although easily managed by dilatation, was a distressing problem; its occurrence to some degree in nearly 30% of the patients was nearly twice that reported after ileal pouch-anal anastomosis.[12] This high rate of stricture may have been partially related to the pelvic radiation that 13 of the patients received.

Four patients who underwent coloanal anastomosis for rectal cancer failed; however, only one failure could be attributed to technical problems, the remainder being due to progression of disease.

Eighteen of the coloanal procedures were performed for adenocarcinoma of the rectum. The margins of resection were wide because the majority of the tumors were in the mid-rectum. Local control was, therefore, excellent; only one patient had a pelvic recurrence (5%). This incidence of local recurrence appears to be somewhat less than the 28% reported by Pilipsher et al.[22] after anterior resection, but the follow-up in our patients was shorter. Distant spread was identified during follow-up in five patients (27%); four of these had a Dukes C_2 lesion at the time of the procedure. The rate of distant recurrence after coloanal anastomosis is slightly higher than the 20% reported by Pilipsher et al.[22] for anterior resection and is likely more indicative of the stage of disease than failure of the operation. These data, therefore, would support the findings of others[16,19,23] that coloanal anastomosis appears to be justified in the management of mid-rectal cancers.

Overall, functional results were good in this group of patients whose mean age was 61 years. Enteric continence was achieved by 84% of the patients; this result compares favorably with those of others who report that more than 75% of patients achieved predictable control of bowel function after coloanal anastomosis.[16,23] Interestingly, these data also compare favorably with those reported after low anterior resection; Mayo and Cullen observed that about 82% of patients could expect a "good result" after anterior resection.[24] Importantly, we found no significant difference in daily stool frequency nor in the incidence of incontinence between the patients operated on for cancer, radiation injury, or benign disease. In the cancer patients, stool frequency and incontinence were not affected by adjuvant radiation therapy.

Urgency and frequency of defecation, however, continue to cause problems after coloanal anastomosis. Several authors have shown that decreased capacity and compliance of the pulled-through proximal colon correlates directly with increased stool frequency and decreased continence.[19,25,26] Keighley and Matheson demonstrated a marked reduction in the neorectal capacity of their coloanal patients compared to preoperative values (64 ± 31 mL *vs.* 268 ± 24 mL).[25] Two recent papers have reported the use of J-shaped preanastomotic colon pouches.[19,27] Not surprisingly, Lazorthes et al. found that capacity was greater when a reservoir was constructed than when the end of the colon was anastomosed directly to the sphincters.[19] They were also able to demonstrate a significant correlation between the maximal tolerable volume of the neorectum and stool frequency. Functional results in their series were good; 86% of the patients had less than three stools per day at the end of 1 year. Based on reports of dramatic improvement in functional results after adaptation of an *ileal* pouch in patients undergoing ileoanal anastomosis,[28] it seems reasonable to expect that the increased capacity and distensibility provided by a *colonic* pouch would similarly decrease urgency and stool frequency after coloanal anastomosis. Although our experience with a preanastomotic pouch was limited to three patients, predictable and reliable function was achieved in each.

Unlike an *ileal* pouch, the colon reservoir need not incorporate limbs longer than 7 or 8 cm. Endorectal mucosectomy may be performed in the standard manner,[17] except that 1–2 cm of rectal mucosa can be spared, *if desired,* in an attempt to improve sensation after surgery. Martin has advocated such an approach in ileoanal patients,[29,30] but we have not found it necessary to leave any rectal mucosa *in situ,* as more than 70% of our patients after ileal pouch-anal anastomosis can distinguish gas from stool after *total* rectal mucosal excision.[21] Finally, impeccable hemostasis, good perfusion of the pouch, a tension-free anastomosis, and adequate drainage will minimize stricture formation and the incidence of pelvic sepsis.

The indications for coloanal anastomosis are limited but are not infrequently encountered. They include severe radiation proctitis causing pain and/or bleeding, and radiation-induced ulcers with or without concomitant fistulae. Coloanal anastomosis is particularly attractive in such patients because 80–90% of the diseased rectum is removed, the most distal 4–5 cm of mucosa is excised, and healthy nonradiated proximal bowel is anastomosed directly to the anal sphincters. The anastomosis, therefore, does not depend on the possibly tenuous blood supply of the remaining radiated rectum for its security.

Another indication for coloanal anastomosis is in patients with large benign tumors, in the lower or middle third of the rectum, which are not amenable to transanal or parasacral resection. Coloanal anastomosis is also useful in patients with a compromised low anterior anastomosis. Finally, coloanal anastomosis is indicated in patients with malignant tumors in the middle third of the rectum in whom an end-to-end colorectostomy, stapled or not, may be fraught with difficulty or hazard due to technical factors. Coloanal anastomosis, however, should *not* be considered an alternative to abdominoperineal resection for cancers in the lower one-third of the rectum, but rather as an alternative to low anterior resection in patients with difficult *middle third* lesions.

In conclusion, coloanal anastomosis is safe, efficacious, and preserves anal continence in a variety of difficult situations in which it is impractical or unwise to attempt anastomosis of the colon directly to the full thickness of the rectum. Moreover, the functional results after coloanal anastomosis are good; the daily stool frequency and rate of continence achieved after coloanal anastomosis compare favorably with those reported after low anterior resection. Importantly, in the management of rectal cancer, local recurrence rates appear to be as low as those reported for anterior resection. These encouraging clinical and functional results of coloanal anastomosis should, therefore, prompt careful but wider application of the technique in selected patients with complicated benign and malignant rectal pathology.

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The Impact of Colonoscopy on the Early Detection of Colonic Neoplasms in Patients with Rectal Bleeding

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A retrospective analysis was made of 372 consecutive patients who underwent colonoscopy because of rectal bleeding. The three distinct patterns of bleeding studied were chronic (224 cases), recent major (93 cases), and acute bleeders (55 cases). In 50% of the cases, colonoscopy detected a lesion other than diverticula. These lesions consisted of several forms of colitis, arteriovenous malformations (AVMs), ulcers, and most importantly, neoplasms in 34% of the cases. In 13% of the cases, an invasive neoplasm was detected and 76% of them were early stage (Dukes A or B). A third of the neoplasms were located proximal to the splenic flexure. Among patients with a negative barium enema, 35% had a neoplasm detected on colonoscopy. These findings were similar for the three distinct patterns of rectal bleeding studied. These data support the need for colonoscopy in all types of rectal bleeders, regardless of the results obtained by BE.

THE INCIDENCE OF colorectal cancer continues to rise and is responsible for more than 60,000 deaths per year in the United States.[1] Despite advances in the treatment of this disease, survival figures in the 1980s differ little from those of 30 years ago.[1,2] Since colon carcinogenesis proceeds slowly through the adenoma-carcinoma sequence,[3] with discernible preneoplastic stages, early detection and removal of precursor lesions is feasible and should reduce colon cancer mortality. Furthermore, since early stage cancers have a good prognosis,[4,5] the identification and resection of these nascent carcinomas should also improve mortality statistics. The need for improved screening of high-risk asymptomatic individuals, as well as the thorough evaluation of symptomatic patients, is therefore evident.

Rectal bleeding is a common symptom of colon polyps as well as colon cancers.[6] In fact, bleeding is thought to be a more frequent symptom of early than late colorectal cancer.[7] Traditionally, it has been taught that the rate and color of bleeding may suggest the site of the lesion (proximal *vs.* distal) or its cause (diverticular *vs.* cancer). Because of this, the need for a complete diagnostic evaluation, including colonoscopy, in different types of rectal bleeders (*i.e.*, acute *vs.* chronic), and the expected yield of adenomatous polyps and early stage cancers from such a thorough evaluation remain unclear.

The purpose of this study was to address these unresolved issues for three distinct patterns of rectal bleeding (chronic, recent major, and acute bleeders) by retrospective analysis of a large population of patients who were colonoscoped because of rectal bleeding.

Patients and Methods

Among patients with rectal bleeding, a consecutive series of 372 patients underwent colonoscopic evaluation at the Surgical Endoscopy Unit (SEU) of the Columbia-Presbyterian Medical Center between the years 1973 and 1986. The patients ranged in age from 3 to 94 years, with a mean of 63 years. Their records, including endoscopic, radiologic, and pathologic reports, were reviewed. According to a protocol implemented in 1973, all patients with rectal bleeding evaluated in the SEU were routinely classified according to their pattern of bleeding at the time of their evaluation as chronic bleeders, recent major bleeders, and acute bleeders.

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The group of chronic bleeders (N = 224) were patients who were referred for colonoscopy because they had experienced multiple episodes of small amounts of bright or dark red blood per rectum (not requiring transfusion), or had been noted to be anemic on routine laboratory studies, which led to the detection of fecal occult blood. These patients underwent elective colonoscopy. Recent major bleeders (N = 93) were those patients who had an episode of significant rectal bleeding requiring emergency admission to the hospital and transfusion. They had spontaneous cessation of their bleeding and were then colonoscoped while still in the hospital, after receiving a standard bowel preparation. Acute bleeders (N = 55) were those patients who were being considered for emergency operation but for whom the usual studies, including angiography in some cases, had not provided a definitive diagnosis. These acute bleeders underwent emergency colonoscopy while actively bleeding, with simply a saline enema to clear the rectum but no formal bowel preparation.

Rigid proctoscopy and barium enema (BE) (postevacuation or double-contrast) were attempted on most of the patients. However, because of the personal preference of the referring physician or patient refusal, 30% of the cases underwent colonoscopy without a prior BE. All 372 patients were included in the study regardless of the results of their precolonoscopy studies. The BE findings were classified as "normal," "abnormal" (including masses, filling defects, strictures, diverticula, or possible lesion), or "not studied." BE results were taken from the official radiologic reports.

At the time of colonoscopy, an attempt was made to examine the cecum when clinically feasible. For elective colonoscopies, if the cecum was not visualized because of inadequate bowel preparation, a second colonoscopic examination was attempted and the findings of the more complete colonoscopy were used. Partial colonoscopies where no abnormalities were discovered were included in the "negative" group.

The diagnosis of carcinoma was proven by colonoscopic biopsy or polypectomy, and further information on their histologic grade was obtained from the surgically resected specimens. Carcinomas were classified into Dukes' original ABC categories.[8] Polyps containing intraepithelial or intramucosal carcinoma or severe dysplasia or atypia were classified as carcinoma *in situ* (CIS). Colonoscopies were done with a variety of colonoscopes manufactured by the Fujinon, Olympus, and Pentax companies.

Statistical comparisons were made by chi square tests of association and ridit analysis.[9] Ridit analysis applies to variables measured on an ordinal scale. It calls for identification of one group as a standard and relates the scale distribution of each study group to the scale distribution of the standard. Since colon neoplasms can be naturally scaled according to increasing order of severity, ridit analysis was used to determine the statistical significance of the observed differences in scale distribution of colonic neoplasms among the three groups of rectal bleeders. We chose the chronic rectal bleeding group as the standard (Tables 3 and 4).

Results

Three hundred and seventy-two patients were examined by colonoscopy. Of these, 106 had a precolonoscopy BE that was normal, 156 were abnormal, and 110 were not studied. The overall colonoscopy and BE results for the study sample are summarized in Table 1.

Overall, colonoscopy visualized a significant lesion in 51% of patients with rectal bleeding. One hundred and twenty eight (34%) of the lesions were neoplastic and of these 61 (48%) were malignant (CIS or invasive tumors).

In the group with a normal BE, 51 (48%) had a significant lesion detected on colonoscopy. The significant lesions consisted of colitis (ischemic, radiation, or inflammation) (7%), arteriovenous malformations (AVM) (5%), colonic ulcers (2%), and neoplastic lesions (35%). Of the neoplastic lesions, three were CIS and eight were invasive tumors. Therefore, in 10% of the patients with rectal bleeding and a normal BE, a malignant lesion was detected on colonoscopy.

In the group with an abnormal BE, consisting of 156 patients, (including diverticula, mass, filling defects, strictures, or those interpreted as "inconclusive" but suggestive of a lesion) 83 (53%) had a significant lesion detected on colonoscopy. Colonic neoplasms were found in 68 of the 156 patients (44%). Eight were CIS and 31 were invasive. Overall, 25% of the patients with rectal bleeding and a positive BE had a malignant lesion detected on colonoscopy.

In the group without a precolonoscopy BE, 56 of the 110 cases (51%) had a significant lesion detected on colonoscopy. In these cases, colonic neoplasms were found in 23 (21%) of the colonoscopies performed. Three were CIS and eight were invasive. Therefore, in 10% of patients with rectal bleeding and no precolonoscopy BE, a malignant lesion was detected on colonoscopy.

Among patients who had a BE performed, there was no statistically significant difference in the colonoscopic detection of neoplasms between patients with a normal BE (37/106) and those with an abnormal BE (68/156).

The neoplastic lesions were found in patients ranging in age from 32 to 87 years (Fig. 1). Most of the neoplastic lesions were found in patients greater than 40 years of age; in patients older than 60, 39% of the cases with rectal bleeding had a neoplasm. The largest percentage of adenomas (23%), CIS (6%), and invasive carcinomas (22%) detected per 10-year age group were in the 7th, 8th, and 9th decades, respectively. The apparent 5- to 10-year lag period between the diagnosis of adenoma-

TABLE 1. *Colonoscopic and Barium Enema Findings in 372 Patients with Rectal Bleeding*

	Colonoscopy Findings											
	Significant Lesions*											
						Carcinoma (Dukes)						
BE Findings	Colitis	AVM	Ulcer	Adenoma	CIS	A	B	C	NA	Total	Diverticula	Negative
Normal (N = 106)	7	5	2	26	3	1	4	1	2	51 (48%)	7 (7%)	48 (45%)
Abnormal† (N = 156)	9	1	5	29	8	8	11	8	4	83 (53%)	54 (34%)	19 (12%)
Not done (N = 110)	13	10	9	12	3	3	4	1	0	55 (50%)	31 (28%)	24 (22%)
Total (N = 372)	29	16	16	67	14	12	19	10	6	189 (51%)	92 (25%)	91 (24%)

* Colitis = due to inflammation, radiation, or ischemia, AVM = arteriovenous malformation; Adenoma = all listed are adenomatous polyps (6 hyperplastic polyps are not included); CIS = *in situ* carcinoma; NA = invasive carcinomas for which a resection was not performed and Dukes staging was therefore not possible; Negative = anal lesions such as hemorrhoids, fissures, warts, etc., or cases of partial colonoscopy (due to fixation, strictures, poor patient compliance, poor bowel prep, or spasm), and totally normal colonoscopies.

† Abnormal = diverticula, mass, filling defects, strictures, or "inconclusive."

tous polyps and carcinomas is consistent with the concept of the adenoma-carcinoma sequence.[3]

The colonoscopic findings as a function of type of rectal bleeding are shown in Table 2. Although the overall percentage of significant lesions detected was similar among the three types of rectal bleeding, there were several individual differences. The proportion of adenomatous polyps detected in the chronic rectal bleeding cases was twice as large as the comparable percentage among the recent major and acute rectal bleeding cases ($p < 0.005$). In contrast, AVMs and diverticula were more frequently detected in the acute and recent major bleeding cases, when compared with the chronic rectal bleeding cases ($p < 0.001$). The frequency of negative colonoscopies in chronic rectal bleeding cases was significantly greater than in the recent major and acute rectal bleeding cases ($p < 0.005$). Based on these analyses, it is unclear which pattern of bleeding signifies a worse prognosis in terms of colonoscopic findings.

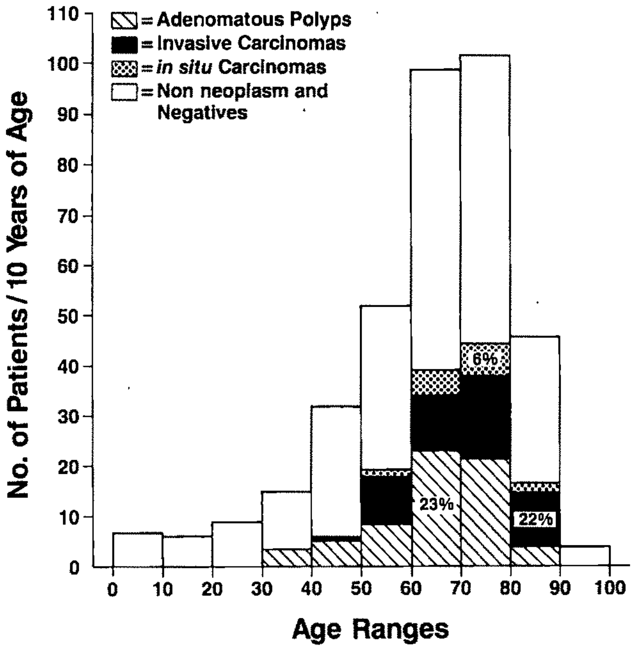

FIG. 1. The per cent distribution of diagnostic categories within each age group is represented by the designated patterns.

In order to better understand the differences in the colonoscopic findings among the three bleeding groups, the colonoscopic findings were grouped and ranked according to degree of severity (Table 3). Based on the assumption that the severity of colonoscopic findings increased in going from negative colonoscopies (least severe), through non-neoplastic findings, adenomatous polyps, *in situ* carcinomas to invasive carcinomas (most severe), ridit analysis did not detect any significant difference in the severity of colonoscopic findings among the three distinct patterns of rectal bleeding ($p > 0.45$). Therefore, although significant individual differences exist in the colonoscopic findings among the three distinct patterns of rectal bleeding, the overall degree of severity in the findings is the same for the three groups.

The percentage of neoplasms potentially amenable to definitive treatment by polypectomy (adenomatous polyps and *in situ* carcinomas) were 64, 68, and 53% for chronic, recent major, and acute bleeders, respectively. Therefore, whatever the pattern of bleeding, colonoscopy, on the average, detected a neoplasm in 34% of the cases of which 64% were potentially curable by polypectomy during their initial diagnostic colonoscopy.

Invasive carcinomas were found in 47 of the 372 patients studied (13%). In 41 of these patients, a surgical resection was performed and staging was therefore possible. The other six patients were too ill, refused to undergo an operation, or had a rectal cancer treated with repeated local fulgurations. Where staging was possible, it was found that 31 of the 41 colorectal cancers (76%)

TABLE 2. *Colonoscopic Findings in 372 Patients with Three Distinct Patterns of Rectal Bleeding*

	Colonoscopy Findings (%)											
	Significant Lesions*											
						Carcinoma (Dukes)						
Bleeding Pattern	Colitis	AVM	Ulcer	Adenoma	CIS	A	B	C	NA	Total	Diverticula	Negative
Chronic (N = 224)	19	5	6	51	7	9	12	8	4	121 (54%)	36 (16%)	67 (30%)
Recent major (N = 93)	5	5	7	11	4	0	4	1	2	39 (42%)	37 (40%)	17 (18%)
Acute (N = 55)	5	6	3	5	3	3	3	1	0	29 (53%)	19 (35%)	7 (13%)
Total (N = 372)	29	16	16	67	14	12	19	10	6	189 (51%)	92 (25%)	91 (24%)

* Colitis = due to inflammation, radiation, or ischemia, AVM = arteriovenous malformation; Adenoma = all listed are adenomatous polyps (6 hyperplastic polyps are not included); CIS = *in situ* carcinoma; NA = invasive carcinomas for which a resection was not performed and Dukes staging was therefore not possible; Negative = anal lesions such as hemorrhoids, fissures, warts, etc., or cases of partial colonoscopy (due to fixation, strictures, poor patient compliance, poor bowel prep, or spasm), and totally normal colonoscopies.

were localized to the bowel wall (Dukes A or B) (Table 4). This high percentage of early stage lesions was noted regardless of the pattern of bleeding. Ridit analysis revealed no significant difference in the severity of neoplastic lesions that were detected among the three types of bleeders.

The location of neoplasms is summarized in Table 5. Although neoplasms were found throughout the entire colon, about a third of both benign and malignant neoplasms were found proximal to the splenic flexure. Among the three patterns of bleeding, chronic bleeders had the lowest, and acute bleeders had the highest percentage of neoplasms located proximal to the splenic flexure. This twofold difference was statistically significant ($p < 0.05$).

Discussion

The exact role of colonoscopy in patients with rectal bleeding has not been fully defined. In people over 40 years of age, the long-term morbidity and mortality associated with rectal bleeding lies in its relationship to colon cancer.[10] Therefore, the evaluation of the role of colonoscopy in rectal bleeders should focus primarily on the impact it will have on the detection and removal of early colonic neoplasms.

Clinical studies[7,11] have shown that in 40–60% of patients harboring one or more colonic neoplasms, the predominant symptom is rectal bleeding. Since clinical[12] as well as pathologic studies[13] have demonstrated a lack of correlation between rectal bleeding and the histologic stage of a tumor, rectal bleeding does not necessarily indicate the presence of an advanced cancer. In fact, bleeding is thought to be a symptom of polyps[13] and early, rather than late, colorectal cancer.[7]

Because the majority of carcinomas, adenomatous polyps, and diverticula occur on the left side of the colon,[11] within reach of a 60-cm flexible sigmoidoscope, the traditional approach to rectal bleeders consists of flexible sigmoidoscopy and BE. This approach would be expected to detect most bleeding colorectal cancers, since most of the colon cancers presenting with a symptom of rectal bleeding are located in the rectosigmoid, as opposed to the right side of the colon.[6,7] Several studies have shown, however, that this approach may be inadequate since 41% and 33% of colonic neoplasms will be

TABLE 3. *Relation Between Bleeding Pattern and Increasing Severity of Colonoscopic Findings*

	Colonoscopy Findings*					
			Neoplastic			
Bleeding Pattern	Negative	Non-neoplastic	Adenoma	*In Situ*	Carcinoma	Total
Chronic (N = 224)	67 (30%)	66 (29%)	51	7	33	91 (41%)
Recent major (N = 93)	17 (18%)	54 (58%)	11	4	7	22 (24%)
Acute (N = 55)	7 (13%)	33 (60%)	5	3	7	15 (27%)
Total (N = 372)	91 (24%)	153 (41%)	67	14	47	128 (34%)

* Colonoscopy findings are arranged in increasing order of severity (negative colonoscopies being the least severe and carcinoma the most severe). Negative = anal lesions (hemorrhoids, fissures, warts, etc.), cases of partial colonoscopy (due to fixation, strictures, poor patient compliance, poor bowel prep, or spasm), and totally normal colonoscopies. Non-Neoplastic = diverticula, colitis, AVM, or ulcer.

TABLE 4. *Relation Between Bleeding Pattern and Pathologic Staging in Carcinoma Patients*

	Dukes' Classification*		
Bleeding Pattern	A (%)	B (%)	C (%)
Chronic (N = 29)	9 (29)	12 (43)	8 (28)
Recent major (N = 5)	0 (0)	4 (80)	1 (20)
Acute (N = 7)	3 (43)	3 (43)	1 (14)
Total (N = 41)	12 (29)	19 (46)	10 (25)

* Dukes A = cancer invading into the submucosa and/or muscularis propia and limited to the bowel wall; Dukes B = cancer invading through the mulscularis propria into the fat or fibrous tissue; Dukes C = cancer metastatic to lymph nodes.

missed by routine and air-contrast BE, respectively.[14–16] Furthermore, 30 to 56% of neoplastic lesions have been found to be proximal to the splenic flexure[17,18] and, therefore, beyond the reach of a standard 60-cm flexible sigmoidoscope.

Previous studies indicate that the diagnostic yield of colonoscopy in detecting malignancy in patients with rectal bleeding ranges from 6.6 to 19%.[17,15] Whether such rates justify routine colonoscopy for all types of rectal bleeders cannot be determined from these studies since they dealt with small numbers of patients,[19] did not differentiate between acute and chronic bleeders,[15] or had conflicting results regarding the early detection of colonic cancers. Depending on the study,[18,20,21] colonoscopy for rectal bleeding detected different percentages (range: 52–78%) of carcinomas confined to the bowel wall.

This study demonstrates the efficacy of colonoscopy in the early detection of colon carcinomas in patients with three major types of rectal bleeding. Our colonoscopy yields of 34% neoplasms (benign plus malignant lesions) and 13% malignant neoplasms among rectal bleeders are consistent with published reports.[15,17] Likewise, the high percentage (>75%) of early stage lesions (limited to the bowel wall) detected by colonoscopy in rectal bleeders in this study has previously been documented,[21] although conflicting reports also exist.[18] To our knowledge, this is the first report to demonstrate the colonoscopic detection of a high percentage of early stage colorectal cancer lesions as a function of the type of rectal bleeding.

The routine use of colonoscopy in rectal bleeders has been questioned by proponents of the flexible sigmoidoscopy and BE combination. Our finding that colonoscopy revealed neoplastic lesions in 37% of patients with a negative BE, and that a substantial number (33%) of these lesions were located proximal to the splenic flexure, demonstrates the enhanced detection-rate that can be achieved with colonoscopy. Furthermore, since colonoscopy can serve as both a diagnostic as well as a therapeutic tool, pedunculated neoplastic polyps and noninvasive carcinomas are potentially curable during the initial diagnostic-therapeutic colonoscopy. In this series, 64% of the neoplasms detected by colonoscopy would have been amenable to this treatment.

Several studies have documented a recent change in the subsite distribution of colon cancer[22] and of benign adenomatous polyps[23] from distal to more proximal lesions. Because of these findings, the adage that 65% of colorectal cancer is within reach of the rigid proctoscope may no longer be tenable. Our results give further credence to this shift of lesions from distal to more proximal sites, and emphasize the increased need for a complete colonoscopic evaluation of rectal bleeders. Our results demonstrate that in rectal bleeders only 51% of the adenomatous polyps and 55% of the malignant neoplasms detected are located in the rectosigmoid region.

The findings of a substantial number of early stage neoplastic lesions located proximal to the splenic flexure in patients with an apparently negative BE were obtained regardless of the pattern of bleeding. These findings suggest that colonoscopy should be performed routinely in all types of rectal bleeders, including acute bleeders. Although some authors have questioned the efficacy of colonoscopy in acute rectal bleeders,[24] we have found it feasible.[25] The present data demonstrate that colonoscopy is not only feasible, but also very effective in detecting early stage colon cancers in acute rectal bleeders. In fact, the need for complete colonoscopic evaluation may be greater in acute bleeders than in chronic bleeders, as one would have expected. The percentage of neoplastic lesions located proximal to splenic flexure in acute bleeders was two times greater than in the chronic bleeders.

Our study population consists of patients with rectal bleeding who were referred for colonoscopy after an ini-

TABLE 5. *Relation Between Bleeding Pattern and Distribution of Neoplasms*

	Site of Neoplasm							
	Proximal				Distal			
Bleeding Pattern	Cecum	Ascending	Transverse	Total	Descending	Sigmoid	Rectum	Total
Chronic (N = 91)	12	3	8	23 (25%)	14	51	3	68 (75%)
Recent major (N = 22)	7	1	1	9 (41%)	4	8	1	13 (59%)
Acute (N = 15)	0	3	5	8 (53%)	3	4	0	7 (47%)
Total (N = 128)	19	7	14	40 (31%)	21	63	4	88 (69%)

tial screening by proctosigmoidoscopy. It is conceivable that a number of the patients who were chronic rectal bleeders never came to colonoscopy for a variety of reasons, including: (1) the screening physician did not feel it was indicated (i.e., pattern of bleeding, age of patient); (2) a cause for the bleeding was discovered on rigid or flexible sigmoidoscopy (hemorrhoids, fissures, warts, or diverticula) and the work-up terminated at that point; or (3) the patient was lost to follow-up after the initial screening. This would result in a selected population in which the detection of anal lesions would be low and colonic lesions, such as neoplasms, higher than in the nonselected population. The possibility of a selection process is not a concern with the cases classified as recent major and acute rectal bleeding, since all patients presenting with these patterns of bleeding underwent colonoscopy. This may explain the higher detection rate of neoplasms in the cases with chronic rectal bleeding when compared to the recent major and acute rectal bleeders.

In this analysis, the negative colonoscopy group includes cases in which the sole finding was an anal lesion such as hemorrhoids, fissures, warts, etc., cases with only a partial colonoscopy (due to external fixation, strictures, poor patient compliance, poor bowel prep, or spasm), and cases with totally normal colonoscopies. Despite this, the frequency of a totally negative colonoscopy (22%) in patients who did not have a precolonoscopy BE was about the same as the frequency of finding a colonic neoplasm. Therefore, if colonoscopy is used as the initial screening tool in rectal bleeders, our data predict that colonoscopy would find a benign or malignant neoplasm in about a third of these patients. This is exclusive of patients with chronic rectal bleeding in whom an etiology for the rectal bleeding was found by precolonoscopy studies, thereby obviating further work-up. A large proportion of these neoplasms (adenoma and CIS), so detected by colonoscopy, would be amenable to a concomitant therapeutic polypectomy.

In summary, this study demonstrates that in patients with rectal bleeding, colonoscopy will often: (1) detect neoplastic lesions not seen by BE (35%); (2) detect neoplastic lesions located proximal to the splenic flexure and threfore beyond the reach of a flexible sigmoidoscope (35%); and (3) detect early stage colon carcinomas (76% of cancers that were staged were Dukes A or B), and thus provide a probable improvement in prognosis. These findings were similar for the three distinct patterns of rectal bleeding studied. Our data, therefore, support the need for colonoscopy in all types of rectal bleeders, regardless of the results obtained by BE. Since a large percentage of the neoplasms (64%) detected during the initial colonoscopy were amenable to a concomitant polypectomy, colonoscopy may be the most prudent diagnostic tool in patients who present with rectal bleeding, especially those at highest risk for the development of colon neoplasms.

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An *In Vitro* Study of the Properties Influencing *Staphylococcus Epidermidis* Adhesion to Prosthetic Vascular Graft Materials

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This study examines the influence of the properties of various vascular graft materials on the bacterial adherence process of two different strains of *Staphylococcus epidermidis* (mucous and normucous producing). Dacron® grafts (both knitted and woven), Teflon® grafts, and Dacron grafts coated with one and two layers of silicone were studied because these materials differ significantly in porosity, hydrophobicity, and surface charge (zeta potential). Graft segments were immersed in ^{3}H-labeled bacteria solution for periods ranging from 5 to 180 minutes and liquid scintillation techniques were used to quantify bacterial adherence. The porous knitted Dacron material had a significantly higher rate of bacterial adherence than either the woven Dacron or Teflon ($p < 0.05$). Silicone coating (either one or two layers) reduced adherence by a factor of four for the knitted Dacron ($p < 0.05$) and by a factor of two for woven Dacron ($p < 0.05$). The mucous producing strain of *S. epidermidis* displayed significantly better adherence to woven and knitted Dacron than the normucous producing strain, but only when 0.25% dextrose was added to the bacteria solution. These findings indicate that the highly porous knitted Dacron grafts have the highest propensity for bacterial adhesion. Graft materials with the most negative zeta potentials are more resistant to bacterial adherence. Silicone coating of Dacron material significantly changed adherence characteristics, suggesting that this may be a viable strategy for protecting implantable medical devices containing materials to which bacteria readily adhere.

INFECTION OF A PROSTHETIC device, especially a vascular graft, is catastrophic. Documented morbidity as high as 75% (for aortic implants) has been associated with graft infection, and limb amputation rates have been reported as high as 50%.[1] Bacteria can be introduced into the graft site at the time of implantation or *via* transient blood bacteremia.[1-3] Whatever the means, bacteria are frequently present in the circulation in sufficient quantities to cause graft infection. Current estimates are that between 1.5 and 7% of all implanted grafts ultimately become infected.[1-3]

When infection occurs, *Staphylococcus epidermidis* is the most prevalent pathogen cultured from implanted medical devices, especially vascular grafts.[3-6] Studies of pathogenic organisms causing infection in implanted medical devices have shown that *S. epidermidis* is the infecting organism in the following percentage of cases: vascular grafts, 60%[4]; hip joints, 50%[5]; and heart valves, 30%.[5] Frequently pathogenic *S. epidermidis* colonies produce a mucoid growth, also known as glycocalyx or slime film, which becomes adherent to the surface of the implanted device.[7] An example of this phenomenon is shown in Figure 1. The production of mucous is believed to facilitate bacterial adhesion and may represent a critical factor in the pathogenesis of medical device infections.[7,8]

A decisive step in the pathogenesis of graft infection is the irreversible attachment of bacteria to the graft surface which, for the purposes of this paper, will be considered adherence. Adherence is determined by complex physicochemical interactions between the graft and the bacteria. These interactions, in turn, are governed by the surface properties of the graft material and the infecting bacteria. Theoretically, the three properties of materials that should have the most influence on bacterial adherence are graft porosity, surface tension, and electronegativity.[9-11]

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Graft porosity is often defined as the water permeability of the graft material (in units of mL H_2O/cm^2 surface area/min) at a transmural pressure gradient of 100 mmHg. In a more general sense, it is an indication of the spacing, or distance between adjacent fibers of the graft material (*i.e.*, the interstitial space). The amount of interstitial space within the graft material matrix will determine how readily blood will pass through the graft wall and how easily tissue surrounding the graft can penetrate the interstices of the material to incorporate it into the body's cellular matrix. The porosity of a synthetic graft is strongly determined by the manufacturing process used (*i.e.*, weaving, knitting, stretching, etc.) and is not necessarily an intrinsic property of the material itself.

The surface tension of a graft material determines how readily an interface can form between the surface of a graft material and another surface (solid or liquid). An interface, or contact, between two surfaces will only occur if it is energetically favorable. Thermodynamic analysis of particle adhesion to surfaces predicts that hydrophobic materials with a low surface tension will result in maximal bacterial adherence.[10]

Electrostatic interactions have been shown to influence the adhesion of bacteria to a substrate.[10,11] When the bacteria and a substrate have the same charge, bacteria will be repelled by an electrostatic force dependent on the electrical potential of each surface. This repulsion results in an energy barrier to adhesion. The electrical potentials of the bacteria and the graft material are due to the presence of charged chemical groups on each surface. For bacteria and synthetic graft material, these charged groups are typically negative and are formed by dissociated acid moieties such as COO^-.[12-14] The charged groups cause the formation of an electrical double layer adjacent to the surface. The electrical potential of the surface is approximated by the electrical potential across the double layer, which is defined as the zeta potential.[13,15]

This study had two primary objectives: to assess the influence of graft material properties on bacterial adherence (*S. epidermidis*) and to determine if this correlated with theoretical expectations. Dacron grafts, both knitted and woven, Teflon (polyetrafluoroethylene) grafts, and Dacron grafts coated with one and two layers of silicone were examined. The material properties of the three grafts and those coated with silicone are shown in Table 1. Previous studies have shown that these synthetic materials have statistically different amounts of bacterial adherence,[9,18-22] but *S. epidermidis* adherence has rarely been tested and the effect of silicone coating on bacterial adherence has not been examined. The second objective was to determine whether a mucous-producing strain of *S. epidermidis* will adhere to vascular grafts more readily than a normucous-producing strain. Adherence data were collected *in vitro*, suspending the bacteria and the grafts in phosphate buffered saline (PBS) to limit bacterial growth during the experiments. For some of the experiments, 0.25% dextrose was added to the PBS solutions because some authors have suggested that sugar molecules facilitate the development of the mucous layer.[12] This low concentration would not support rapid bacterial growth but would provide a substrate for mucous production. Adherences were examined quantitatively by using radiolabeled bacteria, and qualitatively by using scanning electron microscopy.

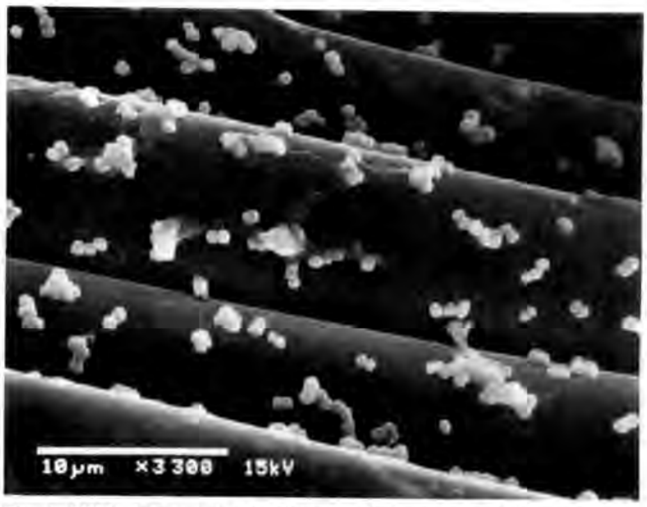

FIG. 1. SEM photograph of a slime-producing strain of *S. epidermidis* (ATCC 14990) attached to the fibers of a woven Dacron graft after 3 hours of immersion in a nutrient broth (0.25% dextrose w/v) solution of 10^8 CFU/mL.

Experimental Methods

Graft Materials

Three different commercially available vascular grafts were used in the experiments: Sauvage Bionit (Bard Biochemical), a knitted Dacron graft; Cooley Low Porosity (Meadox Medical), a woven Dacron graft; and Gortex

TABLE 1. *Graft Material Properties*

Material	Surface Tension[16] (dynes/cm)	Zeta Potential[17] (mv)	Porosity* (mL/min/cm²)
Dacron® (PET)†	43	−9	1500 (knitted) 50 (woven)
Teflon® (PTFE)	18.5	−17	1
Silicone	24	−15 to −21	—

* Porosities for the Dacron grafts were obtained from the respective manufacturers.

† Both Dacron and Teflon are registered trademarks of DuPont.

(W. R. Gore & Associates), a Teflon graft that has been stretched to produce a microporous structure consisting of nodes of polytetrafluoroethylene (PTFE) interconnected by thin fibrils. Additionally, woven and knitted Dacron grafts were dip coated with silicone (polydimethylsiloxane).

Graft Preparation

PTFE graft segments were cut to an approximate length of 2 cm. The crimped graft segments were cut to lengths that reflected a 2-cm length in their uncrimped or elongated state. The degree of crimping was determined by taking the weight ratio of crimped graft to uncrimped graft (obtained from the manufacturers). All grafts had inside diameters of 6 mm. The outside diameters were 7 mm, 6.5 mm, and 7.27 mm for the knitted Dacron, woven Dacron, and PTFE grafts, respectively.

Silicone Coating Procedure

The solution used to coat the Dacron grafts was prepared from Cardiomat 40, made by Kontron Cardiovascular. This is an ultrapure silica-free (or filler-free) solution of 50% (w/v) room temperature vulcanizing polydimethylsiloxane (PDMS) in 2/1 THF-dioxane. The solution was subsequently diluted further with THF-dioxane to approximately 27% PDMS. This dilution yielded the most uniform coat of silicone on both types of Dacron.

The graft segments were completely immersed for 5 minutes and then hung vertically to dry for 24 hours. If a graft was to receive a second coat, it was dried for only 30 minutes and then reimmersed. Porosities of the silicone-coated graft materials were measured at a transmural pressure gradient of 100 mmHg.

Bacteria

The bacteria used in the experiments were two different American Type Culture Collection (ATCC) strains of *S. epidermidis:* 14990 (a mucous-producing strain) and 12228 (a nonmucous-producing strain). Each strain was subcultured onto agar plates and stored at 4 C. This procedure was repeated several days before each experiment.

Preparation of ^{3}H-Labeled Bacteria Solution

Bacteria were transferred sterilly from an agar plate (containing cells that had been recultured the previous day) to Mueller-Hinton Broth (Difco Laboratories, Detroit, MI). ^{3}H-Thymidine (ICN Radiochemicals, Irvine, CA), having a total activity of 0.5 μCi, was then added to this solution. The solution was incubated overnight at 37 C, with the ^{3}H-Thymidine becoming incorporated into the bacterial DNA.

The next day, the bacteria were washed and resuspended in 0.1 N phosphatase buffered saline (PBS), pH 7.4, to produce a solution with an approximate concentration of $1–5 \times 10^8$ CFU/ml. Measurement of the final supernatant for radioactivity yielded values not statistically above background, indicating that ^{3}H-label had been well-incorporated into the bacteria.

The concentration of organisms in the bacteria-PBS solution was determined by measuring the turbidity of the solution at 440 μm using a Johnson Laboratories dual beam spectrophotometer. A standard curve of bacterial concentration *versus* optical density for the two strains was developed using a Coulter particle counter (Coulter Electronics model ZBI, with a 30μm aperture tube).

To determine the concentration of radioactivity (cpm/mL) in the solution, 5 1-mL samples of each bacterial solution were saved for liquid scintillation counting. By dividing the bacterial concentration by the radioactive concentration, the number of bacteria per radioactive count could then be determined.

In Vitro *Bacterial Adherence*

The bacterial solutions were kept at 37 C and mildly agitated. For the dextrose experiments, a concentration of 0.25% w/v dextrose was mixed into each solution immediately prior to graft immersion. Graft segments were completely immersed in a stable horizontal position.

Graft segments were removed from the bacterial solution after intervals of 5, 10, 20, 30, 40, 50, 60, 80, and 180 minutes and then washed in PBS to remove nonadherent bacteria. The specimens were transferred to scintillation vials containing 5 mL of 0.1 N NaOH and vortexed to remove and lyse adherent bacteria.[18] As a control mechanism, the background activity of the graft segments was determined by immersing uncontaminated segments under similar conditions. All the vials of NaOH solution were adjusted to a pH of 7 using dilute HCl.

Graft segments were then removed from the vials and 15 mL of water accepting xylene-based liquid scintillation cocktail (Aquasol, New England Nuclear) was added. The radioactivity of the bacteria in each vial was measured using a Hewlett-Packard Model 2405 Scintillation Counter. Counting time for all samples was 4 minutes. Counting efficiency was approximately 28%.

Calculation of Number of Adherent Bacteria

Absolute values for adherent bacteria were determined using the equation:

$$\text{\# of adherent bacteria} = \frac{\text{weight 2 cm graft segment} \times \text{count} - \begin{pmatrix}\text{background of}\\ \text{uncontaminated}\\ \text{graft segment}\end{pmatrix} \times (\text{\#bac/count})}{\text{weight sample graft}}$$

Adherence was expressed as bacteria per unit surface (cm^2) and bacteria per unit weight (gm) for 2 cm lengths.

Scanning Electron Microscopy

Graft segments were immersed in bacterial solutions (not containing the ^{3}H-thymidine label) using the procedure previously described. Upon removal from the bacterial solution, the graft segments were washed once in PBS and then fixed for 24 hours in a solution containing 2.5% glutaraldehyde and 0.1 N sodium cacodylate buffer. Samples were then postfixed by immersion in a 1% buffered osmium tetroxide solution for 3 hours. The graft segments were then washed with distilled water, immersed in 1% thiocarbohydride for 20 minutes, and then rewashed. The samples were dehydrated in graded solutions of ethanol and then critically point-dried in a Tousimis Model 780 dryer (Tousimis Research Corp., Rockville, MD). They were then mounted on metal stubs, sputter-coated with gold palladium, and examined on an Amray 1200B Scanning Electron Microscope (Amray, Inc., Bedford, MA).

Statistical Analysis

Data were compared for statistical significance with analysis of variance and the two-tailed Student's t-test. P values of <0.05 were considered significant.

Results

Adherence for the knitted Dacron was roughly four times that of either the PTFE or woven Dacron per surface area throughout the experiment (Fig. 2). This difference was statistically significant ($F = 3.24$, $p < 0.05$) for all time periods. While there was no significant difference between the PTFE and the woven Dacron, the PTFE tended to have a lower adherence for the first 30 minutes of contact with the bacterial solution.

When woven Dacron grafts were coated with a single layer of silicone, porosity was lowered by a factor of 6 ($p < 0.05$), whereas for the knitted Dacron, porosity was not significantly changed. The double silicone coating decreased the porosity of both types of Dacron grafts to values approaching zero. Silicone coating of knitted Dacron grafts lowered bacterial adherence by approximately a factor of four for all time periods (Fig. 3A), while adherence to the woven Dacron was lowered by a factor of two (Fig. 3B). These differences were statistically significant for both materials ($p < 0.05$); there were no statistically significant differences, however, in the

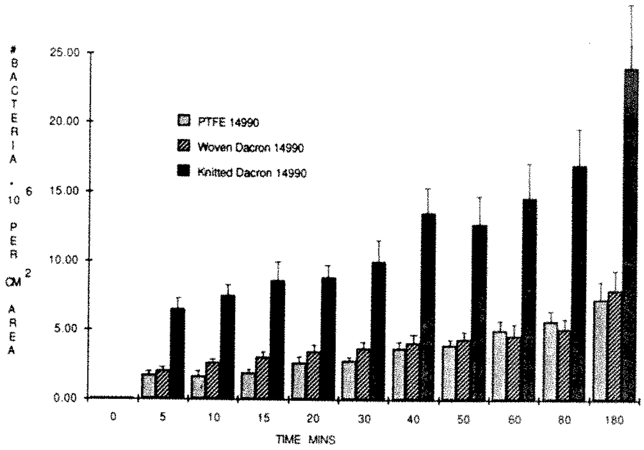

FIG. 2. Bacterial adherence per cm^2 surface area for PTFE, woven and knitted Dacron (N = 11).

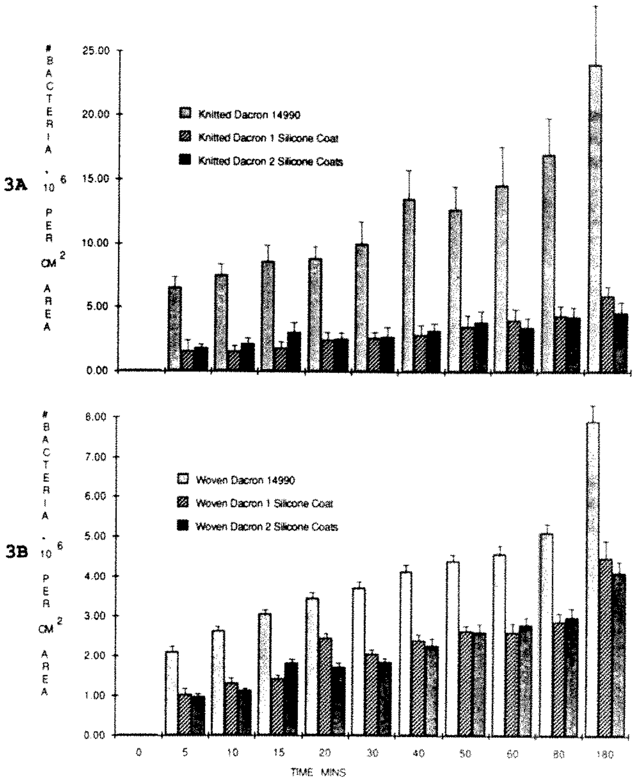

FIG. 3. Bacterial adherence (ATCC 14990) per cm^2 surface area for (*A*) knitted Dacron uncoated, and coated with one and two layers of silicone (N = 7) and (*B*) woven Dacron uncoated, and coated with one and two layers of silicone (N = 7).

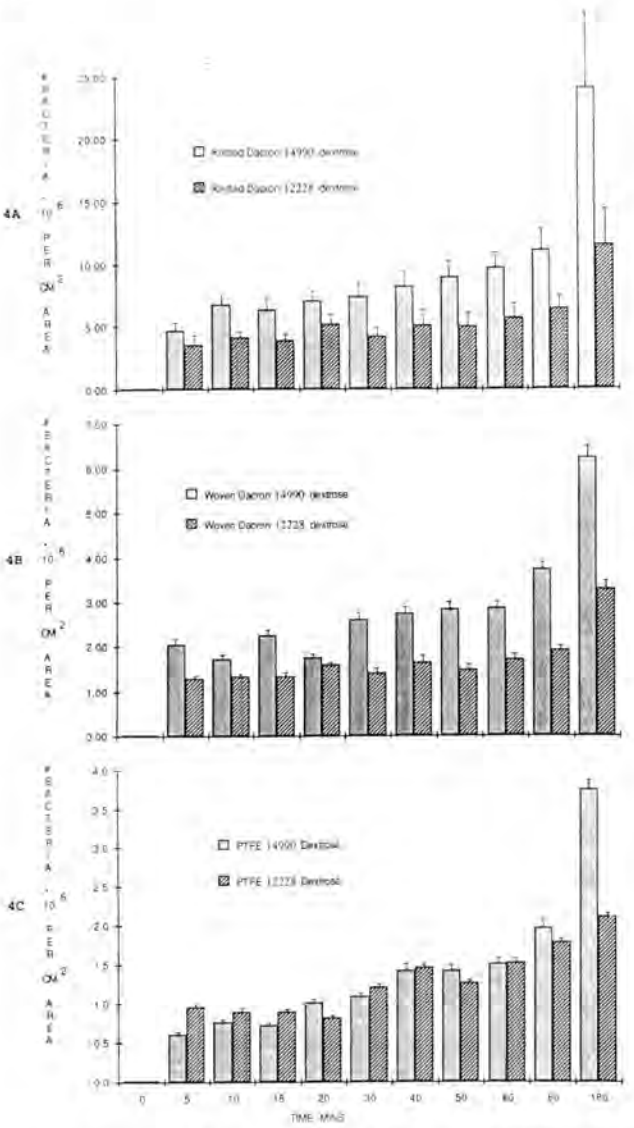

FIG. 4. Adherence of *S. epidermidis* strains 14990 and 12228 grown in PBS with 0.25% dextrose added to (*A*) knitted Dacron (N = 4), (*B*) woven Dacron (N = 4), and (*C*) PTFE (N = 4).

single *versus* double silicone-coated grafts in spite of the differences in porosity. When the adherence of single-coated knitted and woven Dacron grafts was compared to the adherence to PTFE, there were no statistically significant differences for any of the three materials at any of the time periods.

No significant difference in adherence existed between the two strains of *S. epidermidis* at any time for any of the three materials in PBS buffer. However, when 0.25% dextrose was added to the bacterial solutions, strain 14990 adhered to woven and knitted Dacron segments in significantly greater ($p < 0.05$) quantities (Figs. 4A and B). Data were inconclusive for the PTFE segments (Fig. 4C).

Adherence values for the graft materials appeared to increase in a nonlinear, almost exponential manner with time. To characterize the time course of bacterial adherence, experimental data were fit (using linear regression) to the first order kinetic equation:

$$A(t) = A_f(1 - e^{-kt})$$

where A(t) is the number of adherent bacteria as a function of time, k is the attachment rate constant, and A_f is the final number of adherent bacteria. Table 2 lists the rate constants and correlation coefficients for each combination of material and bacterial strain. There was good agreement between the experimental and calculated data for each material. The rate constants were highest for siliconized materials, because the silicone adherence curves had the lowest maximal value and the rate constant reflects how quickly the adherence curve for each material reaches its maximum value. There was no correlation between rate constants and bacterial strain.

Scanning Electron Microscope Observations

The qualitative observations from the scanning electron microscope (SEM) photographs agreed with the quantitative results. Figures 6A and B are SEM photographs of a sample of PTFE that had been immersed in a solution of *S. epidermidis* (14990, ~10^8 CFU/mL) for 10 and 30 minutes. In contrast, samples of knitted Dacron immersed for 10 and 30 minutes in the same solution (Fig. 5A and B) have larger numbers of adherent bacteria.

Although bacteria adhere in concentrated patches to both knitted and woven Dacron by 30 minutes, bacteria have attached individually with a discrete distance between cells even in these dense patches. For the knitted Dacron, many of the dense patches occur on recessed fibers, sheltered from the surface and any hydrodynamic shear forces. In contrast, the close packing of fibers in

TABLE 2. *Correlation Coefficients and Rate Constants from Kinetic Model*

Material	Bacterial Strain	Correlation Coefficient	k $(min)^{-1}$
PTFE	14990	−0.98	0.0175
Woven Dacron	14990	−0.99	0.0093
Knitted Dacron	14990	−0.99	0.0120
Woven Dacron: Silicone × 1	14990	−0.90	0.0097
Woven Dacron: Silicone × 2	14990	−0.98	0.0140
Knitted Dacron: Silicone × 2	14990	−0.92	0.0240
PTFE	14990 Dextrose	−0.98	0.0071
Woven Dacron	14990 Dextrose	−0.93	0.0068
Knitted Dacron	14990 Dextrose	−0.98	0.0048
PTFE	12228 Dextrose	−0.93	0.0168
Woven Dacron	12228 Dextrose	−0.90	0.0043
Knitted Dacron	12228 Dextrose	−0.91	0.0052

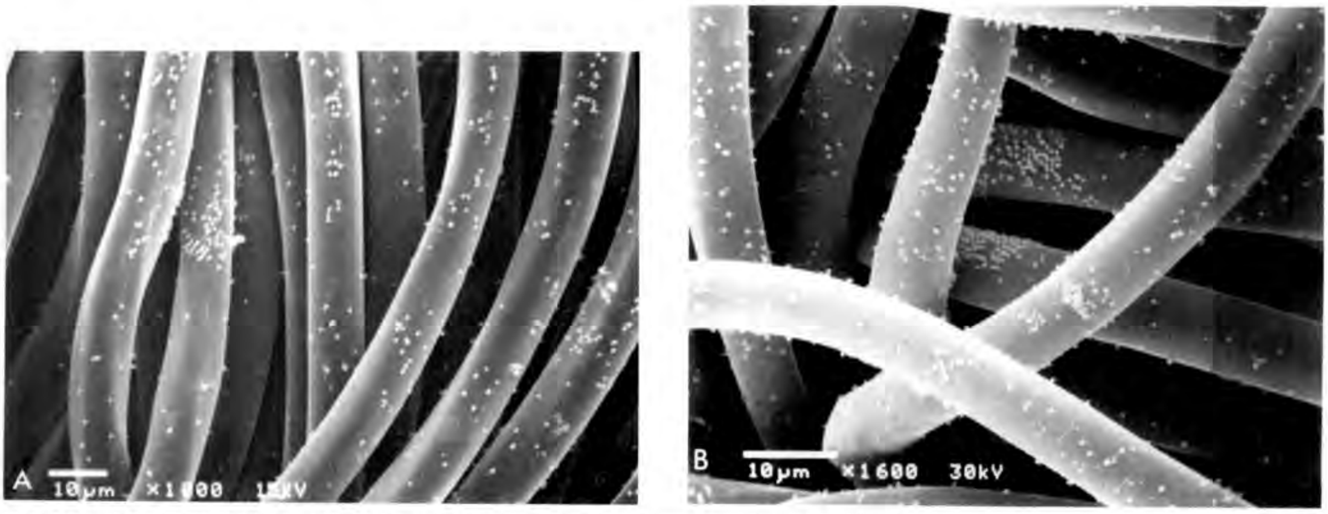

FIG. 5A and B. *A*. SEM photograph of a segment of knitted Dacron immersed for 10 minutes in a solution of *S. epidermidis* (14990, ~10^8 CFU/mL); *B*. SEM photograph of a segment of knitted Dacron immersed for 30 minutes in a solution of *S. epidermidis* (14990, ~10^8 CFU/mL).

the woven Dacron samples does not allow bacteria to pass as readily into the interstitial spaces.

When the grafts were immersed for 3 hours in a nutrient solution containing 10^8 CFU/mL of the mucous-producing strain (14990), bacteria on the grafts had a mucous film surrounding them and appeared to be in aggregated groups, connected to the surface *via* the mucous film (Fig. 1).

Discussion

Graft porosity is a major factor affecting bacterial adherence. The highly porous knitted Dacron graft material has the greatest propensity for bacterial adherence. Woven Dacron, which is much less porous, has significantly less bacterial adherence even though the other material properties are identical. Hydrophobic, electronegative materials, such as PTFE and silicone, have less bacterial adherence than Dacron, which has the highest surface tension and zeta potential. Silicone coating the woven and knitted Dacron grafts alters all three of the prementioned properties and significantly reduces bacterial adherence.

Graft materials that are porous provide bacteria with greater access to the interstices of the graft, effectively increasing the available surface area for adherence. We expected silicone coating to decrease the access to the interstitial spaces of knitted Dacron and woven Dacron grafts and subsequently demonstrated a significant reduction in bacterial adherence to both knitted and woven graft samples after such treatment. This reduction was significantly greater for the knitted Dacron, which could be expected to have the larger reduction in interstitial surface area from silicone coating. However,

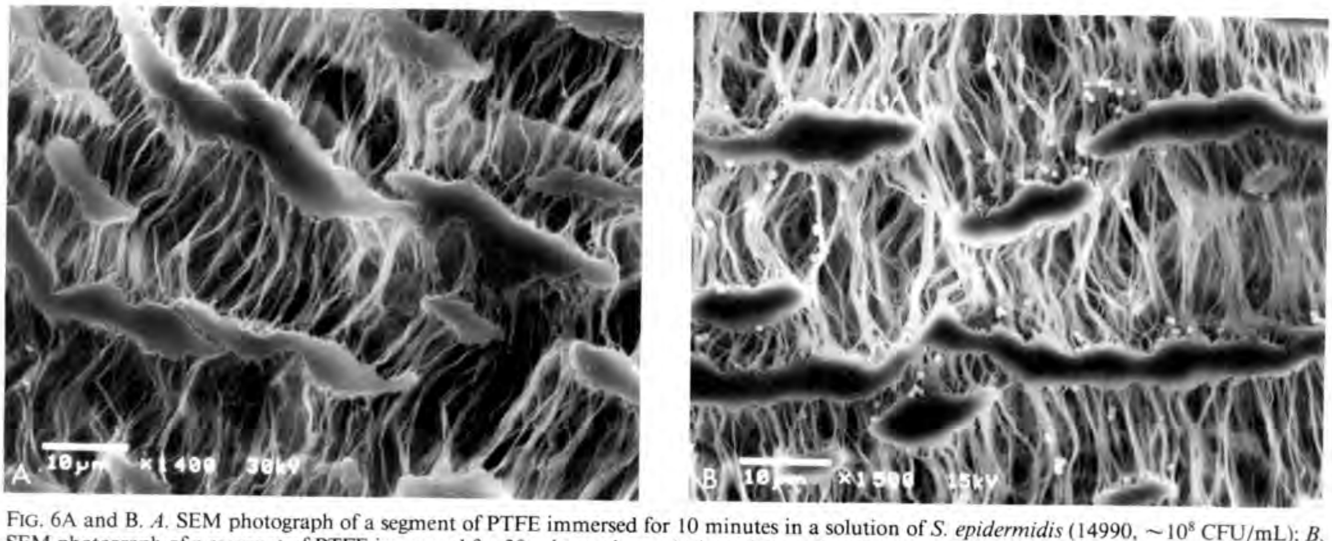

FIG. 6A and B. *A*. SEM photograph of a segment of PTFE immersed for 10 minutes in a solution of *S. epidermidis* (14990, ~10^8 CFU/mL); *B*. SEM photograph of a segment of PTFE immersed for 30 minutes in a solution of *S. epidermidis* (14990, ~10^8 CFU/mL).

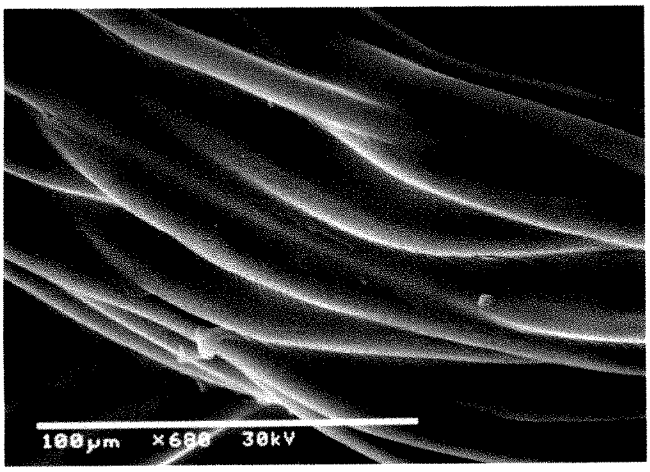

FIG. 7. SEM photograph of a segment of knitted Dacron graft coated with one layer of silicone.

there was no statistically significant difference in the measured porosities of the single silicone-coated knitted Dacron and the uncoated knitted Dacron graft segments, although there were significant differences in bacterial adherence. Additionally, while the porosity of the double silicone-coated knitted Dacron was reduced to almost zero, no significant difference existed in amounts of bacterial adherence between the single and double silicone-coated knitted Dacron graft segments. Unfortunately, porosity measurements, which use water, are probably not the most appropriate measure of the interstitial space between graft fibers, especially if one is interested in correlating bacterial adherence with surface area available for bacterial adherence. The SEM photographs show the silicone filling the interfibril spaces and suggest that surface area for bacterial adherence is decreased (Fig. 7).

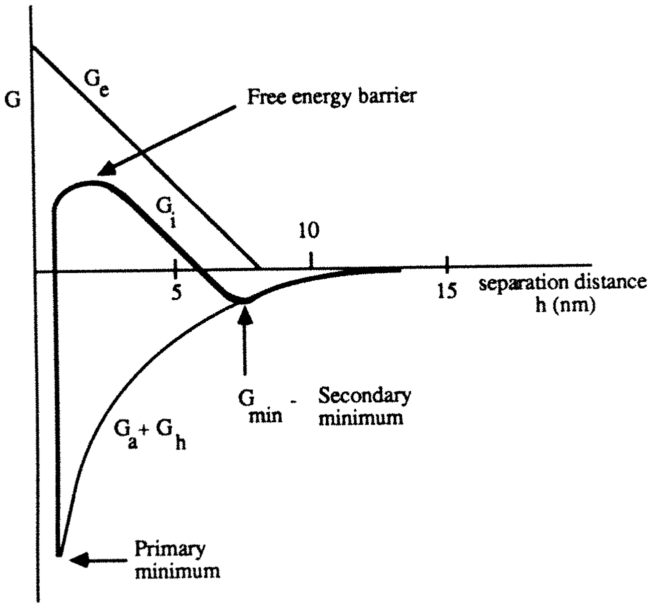

FIG. 8. Interactive free energy *versus* separation distance for a changed spherical colloidal particle approaching a like-charged planar surface.

Results from several other studies have shown that bacterial adherence rates for the highly porous knitted Dacron vascular grafts are significantly greater for a variety of bacteria than for the other lower porosity graft materials.[19-22] Also, porous materials were shown by Merrit et al.[23] to have significantly higher rates of infection than nonporous materials when implanted subcutaneously in mice that were challenged with *Staphylococcus aureus.*

Theoretically, bacterial adhesion to a surface depends on the electronegativity and hydrophobicity of the type of bacteria and on the surface characteristics of the material. These interactions can be analyzed using the three main forces responsible for surface-particle interactions in liquids.[15] The attractive forces are van der Waals (or London Dispersion forces) and hydrophobic interactive forces, which occur when both surfaces tend to repel water. Repulsion is caused by electrostatic forces occurring when the bacteria and surface have the same electrical charge. The summation of forces is defined as the interactive free energy, or G_i, which can be expressed as:

$$G_i = G_a + G_h + G_e$$ [15,24]

where G_a, G_h, and G_e are the van der Waals, hydrophobic, and electrostatic forces, respectively. A schematic representation of G_i is shown in Figure 8.

Adhesion occurs when the free energy of the system is minimized, which is when work must be done to separate an organism that has contacted a surface.[25] Theoretically, there are two discrete distances in which free energy is minimized.[26,27] As indicated in Figure 8, these distances are known as the primary and secondary minimums. At the primary minimum, the particle is sitting very close to the surface (<1 nm). Attachment at this point is irreversible (*i.e.*, adherence) because the particle is in a very deep energy trough. However, in order to be captured in a primary minimum, a particle striking the surface must have sufficient kinetic energy to overcome the free energy barrier resulting from electrostatic repulsive forces. At the secondary minimum, the particle is sitting in a minor energy trough (prior to the free energy barrier) and is only loosely attached to the surface. Because electrical repulsion forces decay more rapidly with distance than dispersion forces, bacteria are attracted to the surface until repulsive become significant.[11,15] An organism will stay at this point, in a metastable or reversible state of adsorption. The degree of reversibility depends on the depth of the energy trough. Detachment is caused by fluid shear forces in the microenvironment of the bacteria. If bacteria can remain in a secondary minimum long enough, they can produce mucous and use this network of polysaccharide fibrils to permanently anchor themselves to a surface.[12,15]

Of the manufactured grafts we examined, PTFE had the lowest degree of bacterial adherence. *S. epidermidis* is hydrophobic.[9] Also, bacteria that produce mucous have a negative surface charge.[11,12] On a theoretical basis, therefore, the *S. epidermidis* used in this study were expected to adhere in greater numbers to the more hydrophobic materials and in lesser amounts to the more electronegative materials.[10,11] PTFE, however, is both hydrophobic and electronegative. The electronegative repulsive force between the bacteria and the material surface clearly outweighed the attractive forces from the hydrophobic interactions between the organisms and the surface.

Other investigators have reported similar results. Abbott et al.[11] and Newmann et al.[10] have also shown that adhesion is inversely proportional to the negative electrical surface charge or zeta potential of bacteria, particularly in solutions with low electrolyte concentrations. Neither of these studies, however, examined *S. epidermidis* interaction with the plastics, Teflon or Dacron. Brown et al.[28] compared PTFE patches to polypropylene mesh patches in abdominal wall repairs complicated by intraoperative contamination with *S. aureus*. The PTFE patches had significantly fewer adherent organisms at removal. Sugarman[19] observed reduced microbial adherence to PTFE for a variety of bacteria with negatively charged surface groups and proposed that the electronegative nature of PTFE was a contributing factor. While Sugarman did not examine *S. epidermidis* adherence, Schmitt and co-workers[21,22] have also examined *S. epidermidis* using a 24-hour innoculation period and reported similar results; PTFE had the lowest number of adherent bacteria of the samples tested. They did not examine silicone-coated grafts.

Further evidence that electrostatic repulsion is important in decreasing bacterial adherence is provided by the results of our silicon coating experiments. When Dacron grafts were coated with silicone, increasing the hydrophobicity and electronegativity, bacterial adherence was significantly reduced. Implanted medical devices made of silicone have been in use since 1959.[29] Although the nonporous structure of silicone has been assumed to be resistant to bacterial adherence, this study is unique in that we were able to show that even porous devices with a silicone coating are relatively resistant to bacterial adherence.

This study also investigated whether bacterial production of a mucous biofilm contributes to the process of bacterial adherence to graft materials. SEM photographs demonstrated the facilitative role of the mucous in the attachment process. Organisms can initially become incorporated into the mucous layer that adherent bacteria produce even before they establish contact with the graft. This allows bacteria to accumulate in large aggregated groupings. Without the mucous film, bacteria only adhered to the surface on an individual basis with a discrete distance between cells. Negatively charged latex particles display similar behavior.[11] This type of discrete adherence is due to electrostatic lateral repulsive forces between particles, which the mucous film seems to be able to minimize. The statistical differences in adherence between the mucous-producing (14990) and non-mucous-producing (12228) strains of *S. epidermidis* also supported the concept of a facilitative role for the mucous film. However, this difference was only manifested when 0.25% (w/v) dextrose was added to the suspending PBS solution, suggesting that bacteria need a minimal concentration of substrate to produce the mucous. This has been previously confirmed and the formation of mucous is assumed to require energy and nutrients.[12,21,22]

The results from this study, as well as others, point to a general conclusion regarding bacterial adhesion to vascular grafts. Optimal resistance to bacterial adherence and infection can be expected from vascular prosthetics, which have properties most similar to those of the native artery or vein. Therefore, a prosthetic graft should have a smooth, relatively nonporous surface that is somewhat electronegative and a surface tension of approximately 25 dynes/cm.[10,30] Presently, the synthetic medical material most closely matching these criteria is silicone, followed by PTFE. Any process that can alter the physical and morphologic properties of a synthetic material to more closely resemble those of living tissue should improve the resistance of that material to infection. One such process, which has already shown potential for reducing graft infection, is the preseeding of the vascular graft with autologous endothelial cells.[31,32] Further studies using absorbable materials for arterial conduits may demonstrate a potential for decreasing the long-term risk of infection.[33]

Finally, as the number of patients who might benefit from the implantation of some form of medical device rises, further studies must be directed toward determining how host, bacteria, and foreign body interact *in vivo*. With this knowledge, it will be possible to devise strategies that will decrease the percentage of devices that must be removed because of chronic infection. Organisms such as *S. epidermidis*, once considered incapable of producing infection, can become pathogenic in individuals with prosthetic devices.[4–8] Additionally, evidence is accumulating that prosthetic devices alter the immune competency of a host.[34,35] Individuals with prosthetic devices probably need prophylactic antibiotic protection during certain events associated with significant bacteremia, but cannot be given continuous treatment without a corresponding increase in the evolution of antibiotic resistant strains of bacteria.[36] Attempts at bonding antibiotics to grafts have shown some promise, but effective drug levels are not maintained for longer than a period of weeks.[37] Over 20 years ago, Folkman and Long[38] demonstrated that drugs could be absorbed by silicone and released over periods of time ranging up to several months. If antibiotics can be absorbed by silicone, this may present another avenue where silicone-coated medical devices will help resist bacterial contamination. For the field of implanted medical devices to evolve to its full potential, more infection-resistant, biocompatible materials need to be developed.

Acknowledgments

The silicone coating procedure we used was developed by Mr. James H. Donachy and Dr. William S. Pierce of the Division of Artificial Organs, Department of Surgery, the Pennsylvania State University. Their assistance was greatly appreciated. This technique is similar to that described by Asher et al.[39] We also thank Drs. John A. Waldhausen and Brian L. Thiele, who reviewed the manuscript and provided guidance throughout these studies.

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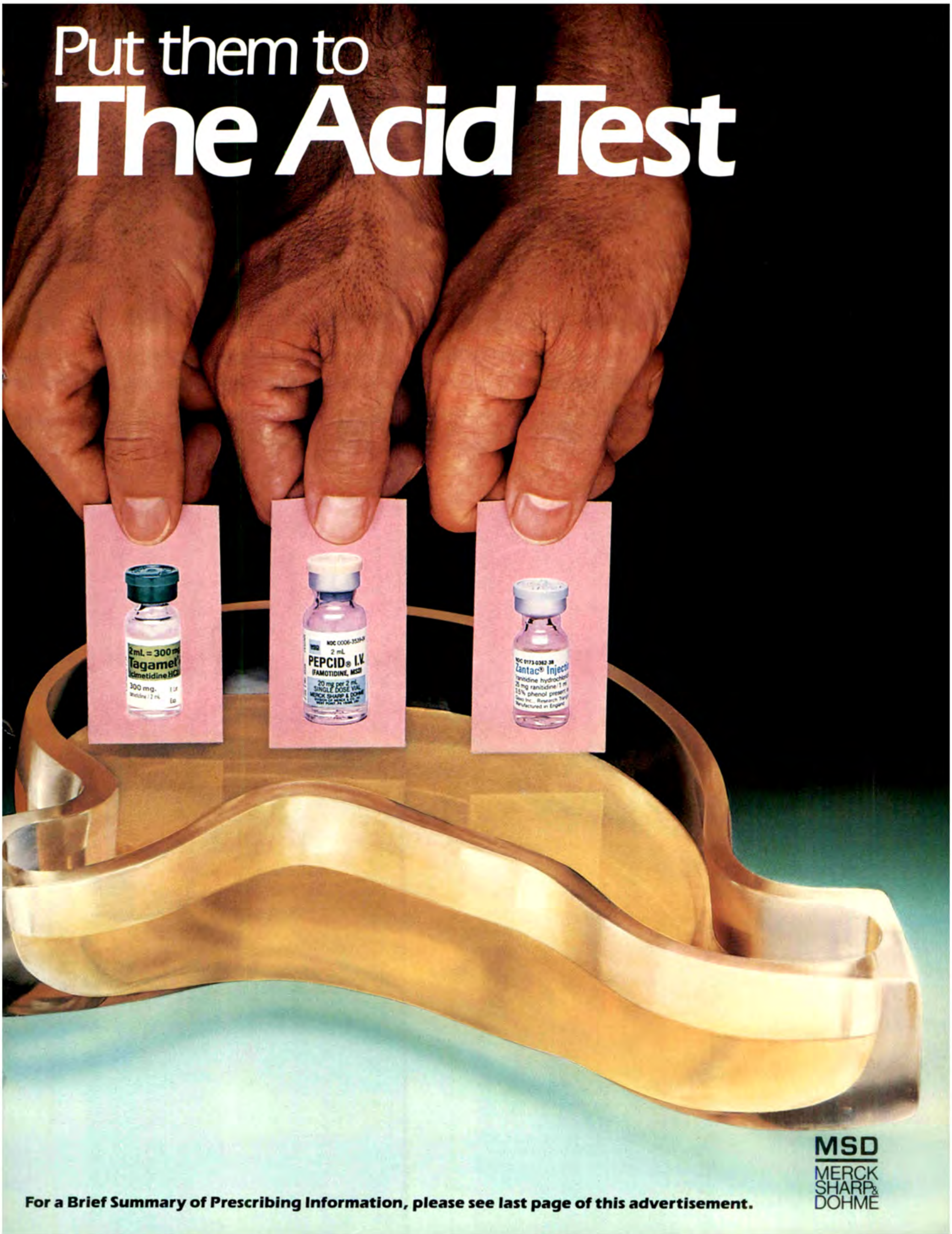

For a Brief Summary of Prescribing Information, please see last page of this advertisement.

Only one H_2 antagonist controls pH for up to 12 hours on a single dose

PEPCID® I.V. (Famotidine, MSD) is indicated in some hospitalized patients with pathological hypersecretory conditions or intractable ulcers or as an alternative to the oral dosage forms for short-term use in patients who are unable to take oral medication.

The recommended dosage is 20 mg q12h. Dosing intervals may need to be prolonged or dosage reduced in patients with severe renal insufficiency (creatinine clearance <10 mL/min) to adjust for the longer elimination half-life of famotidine. PEPCID I.V. is contraindicated in patients who are hypersensitive to any component of this medication. The adverse reactions reported for PEPCID Tablets may also occur with PEPCID I.V. In addition, transient irritation at the injection site has been observed with PEPCID I.V.

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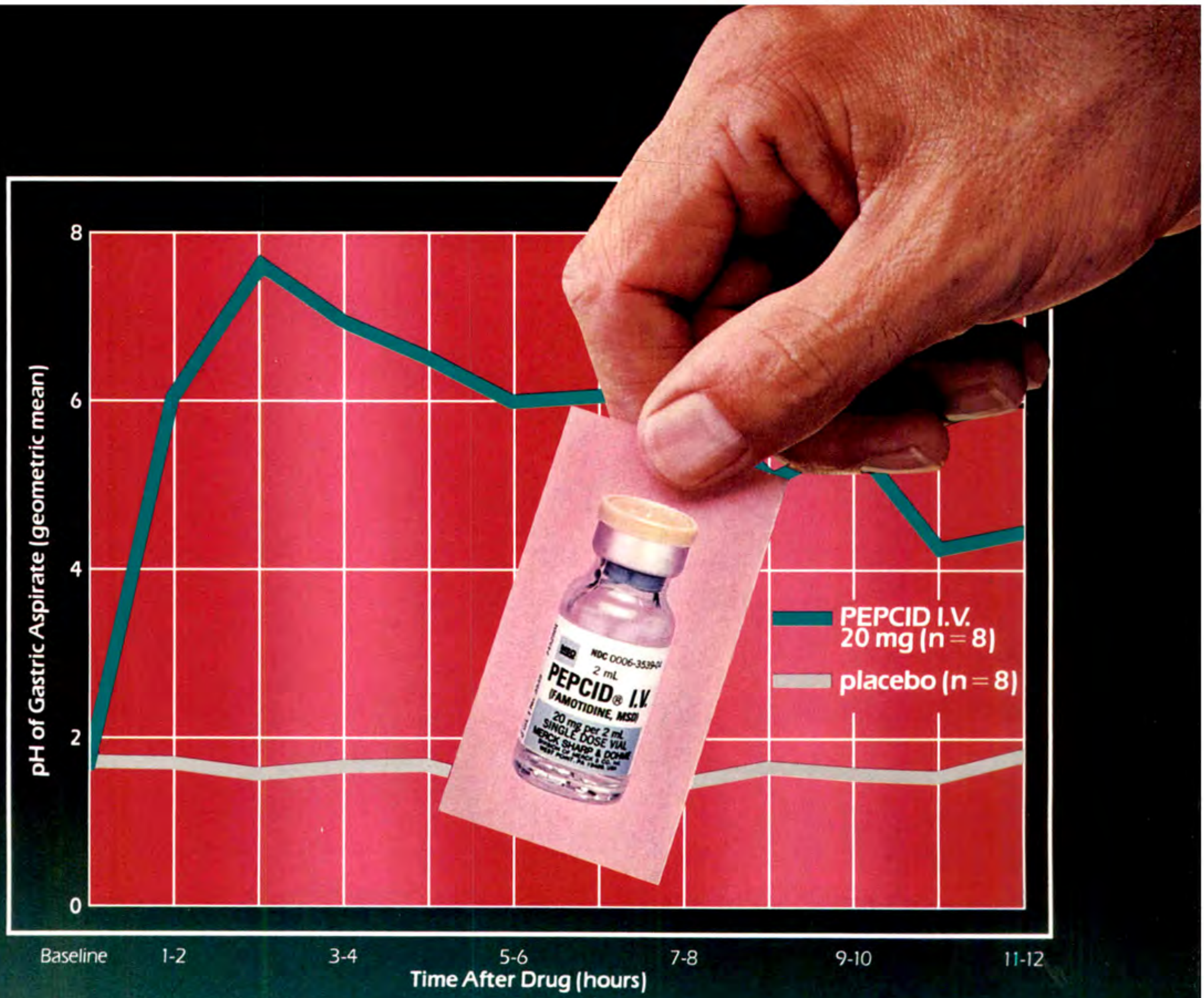

A double-blind, placebo-controlled study[1] involving eight volunteer hypersecretor subjects. The pH of gastric aspirates was measured hourly for 12 hours following single intravenous doses. PEPCID I.V. maintained the mean gastric pH above 4.0 at all time points throughout the 12-hour period with one 20-mg I.V. dose.

[1] Ryan, J.R. et al.: Comparison of effects of oral and intravenous famotidine on inhibition of nocturnal gastric acid secretion, Am. J. Med. 81 (Suppl. 4B): 60-64, October 24, 1986.

INJECTION, 20 mg/2 mL

q12h **Pepcid® IV**

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20 mg and 40 mg

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Oral Suspension|MSD)
40 mg per 5 mL

INJECTION
Pepcid® IV
(Famotidine|MSD)
20 mg per 2 mL

Contraindications: Hypersensitivity to any component.

Precautions: ***General:*** Symptomatic response to therapy does not preclude the presence of gastric malignancy.

Patients with Severe Renal Insufficiency: Longer intervals between doses or lower doses may be needed in patients with severe renal insufficiency (creatinine clearance <10 mL/min) to adjust for the longer elimination half-life of famotidine (see Clinical Pharmacology and Dosage and Administration sections of Prescribing Information).

Information for Patients: The oral suspension should be shaken vigorously for 5-10 seconds prior to each use, and unused constituted oral suspension should be discarded after 30 days.

Drug Interactions: No drug interactions have been identified. Compounds tested in man include warfarin, theophylline, phenytoin, diazepam, aminopyrine, and antipyrine.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In rats and mice given oral doses up to approximately 2500 times the recommended human dose for active duodenal ulcer, there was no evidence of carcinogenic potential, no evidence of a mutagenic effect, and fertility and reproductive performance were not affected.

Pregnancy: *Pregnancy Category B*—There are no adequate or well-controlled studies in pregnant women. Use during pregnancy only if clearly needed.

Nursing Mothers: It is not known whether famotidine is secreted into human milk; however, it is secreted into the milk of lactating rats. A decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in children have not been established.

Use in Elderly Patients: No dosage adjustment is required based on age but may be necessary in severe renal impairment (see Clinical Pharmacology section of Prescribing Information).

Adverse Reactions: The adverse reactions listed below have been reported during domestic and international clinical trials in approximately 2500 patients. In the placebo-controlled clinical trials, the incidence of adverse experiences with PEPCID Tablets, 40 mg at bedtime, was similar to that with placebo.

Incidence Greater than 1%: The following adverse reactions have been reported to occur in more than 1% of patients on therapy with PEPCID in controlled clinical trials and may be causally related to the drug: headache (4.7%), dizziness (1.3%), constipation (1.2%), and diarrhea (1.7%).

Causal Relationship Unknown: The following other adverse reactions have been reported in clinical trials. While a causal relationship could not be established for these infrequently reported events, causality cannot be excluded. *Body as a Whole*—Fever, asthenia, fatigue. *Cardiovascular*—Palpitations. *Gastrointestinal*—Nausea, vomiting, abdominal discomfort, anorexia, dry mouth, liver enzyme abnormalities. *Hematologic*—Thrombocytopenia. *Hypersensitivity*—Orbital edema, conjunctival injection. *Musculoskeletal*—Musculoskeletal pain, arthralgia. *Nervous System/Psychiatric*—Paresthesias; grand mal seizures (single report); psychic disturbances including depression, anxiety, decreased libido, hallucinations (single report); insomnia; somnolence. *Respiratory*—Bronchospasm. *Skin*—Alopecia, acne, pruritus, rash, dry skin, flushing. *Special Senses*—Tinnitus, taste disorder.

The adverse reactions reported for PEPCID Tablets may also occur with PEPCID Oral Suspension or PEPCID I.V.; in addition, transient irritation at the injection site has been observed with PEPCID I.V.

Management of Overdosage: There is no experience to date with deliberate overdosage. Up to 640 mg/day have been given to patients with pathological hypersecretory conditions with no serious adverse effects. In the event of overdosage, treatment should be symptomatic and supportive. Unabsorbed material should be removed from the gastrointestinal tract, the patient should be monitored, and supportive therapy should be employed.

Dosage and Administration: ***Duodenal Ulcer:*** The recommended adult oral dosage for active duodenal ulcer is 40 mg h.s.; most patients heal within 4 weeks, and it is rarely necessary to use the full dosage for longer than 6 to 8 weeks. A regimen of 20 mg b.i.d. is also effective. For maintenance therapy, the recommended oral dosage is 20 mg h.s.

Pathological Hypersecretory Conditions (e.g., Zollinger-Ellison Syndrome, Multiple Endocrine Adenomas): The dosage varies with the individual patient; the recommended adult oral starting dosage is 20 mg q6h, but some patients may require a higher starting dosage. Dosages should be adjusted to individual patient needs and continued as long as clinically indicated; up to 160 mg q6h have been administered to some patients with severe Zollinger-Ellison syndrome.

Oral Suspension: The Oral Suspension may be substituted for Tablets for those patients who cannot swallow tablets.

Directions for Preparing PEPCID Oral Suspension: Prepare suspension at time of dispensing. Slowly add 46 mL Purified Water. Shake vigorously for 5-10 seconds immediately after adding the water and immediately before use.

Stability of PEPCID Oral Suspension: Unused constituted oral suspension should be discarded after 30 days.

Intravenous Administration: In some hospitalized patients with pathological hypersecretory conditions or intractable ulcers, or in patients who are unable to take oral medication, the recommended intravenous dosage is 20 mg q12h. For preparation of solutions for injection or infusion and for compatible diluents, please see Prescribing Information. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

Concomitant Use of Antacids: Antacids may be given concomitantly if needed.

Dosage Adjustment for Patients with Severe Renal Insufficiency: In patients with severe renal insufficiency (creatinine clearance less than 10 mL/min), the elimination half-life of famotidine may exceed 20 hours, reaching approximately 24 hours in anuric patients. Although no relationship of adverse effects to high plasma levels has been established, to avoid excess accumulation of the drug, the dosage may be reduced to 20 mg h.s. or the dosing interval may be prolonged to 36 to 48 hours as indicated by the patient's clinical response.

How Supplied: Tablets, containing 20 mg or 40 mg famotidine, with hydroxypropyl cellulose, hydroxypropyl methylcellulose, iron oxides, magnesium stearate, microcrystalline cellulose, starch, talc, and titanium dioxide as inactive ingredients, in bottles of 30 and unit-dose packages of 100; Oral Suspension, containing per 5 mL after constitution with 46 mL Purified Water, 40 mg famotidine, with citric acid, flavors, microcrystalline cellulose and carboxymethylcellulose sodium, sucrose, and xanthan gum as inactive ingredients, and sodium benzoate 0.1%, sodium methylparaben 0.1%, and sodium propylparaben 0.02% added as preservatives, in bottles of 400 mg famotidine for constitution; Solution for intravenous injection, containing 10 mg famotidine per mL, with L-aspartic acid 4 mg, mannitol 20 mg, and water for injection q.s. 1 mL as inactive ingredients, and benzyl alcohol 0.9% added as preservative to the multidose vial, as 10x2-mL single-dose vials and as 4-mL vials.

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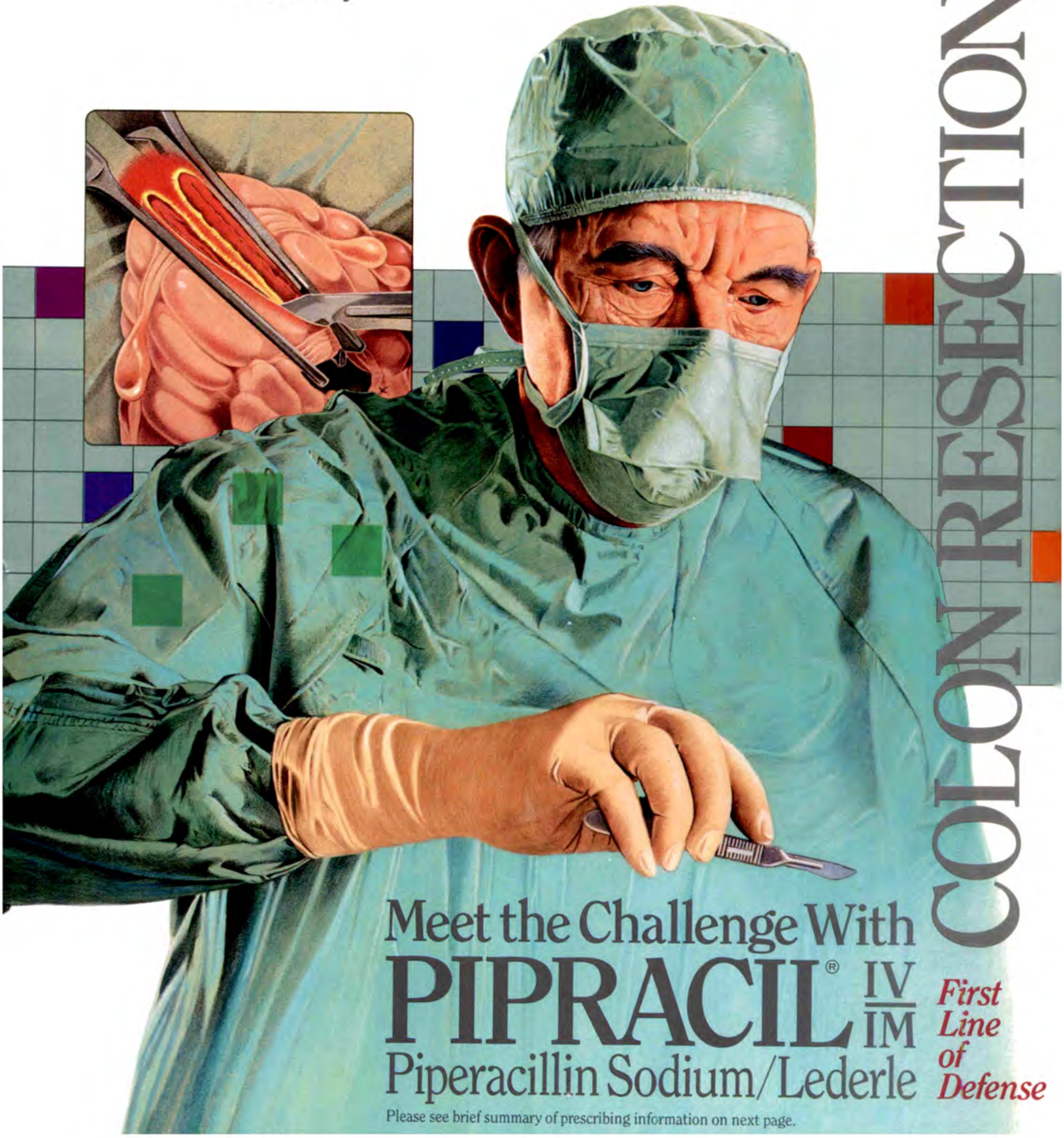

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Mefoxin	89%

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Mefoxin	11.9 ± 1.9 days

[a] Includes gastrointestinal, biliary tract, and other intra-abdominal surgery.
[b] Satisfactory response: no evidence of bacterial infection within 3 to 10 weeks after the last dose of antibiotic.
[c] Time from administration of the first dose of study medication to time of hospital discharge.

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[a] Although a useful guide, *in vitro* activity does not necessarily correlate with clinical response.
[b] Isolated from surgical wounds.

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WARNINGS: Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients receiving therapy with penicillins. These reactions are more apt to occur in persons with a history of sensitivity to multiple allergens.

There have been reports of patients with a history of penicillin hypersensitivity who have experienced severe hypersensitivity reactions when treated with a cephalosporin. Before initiating therapy with PIPRACIL® sterile piperacillin sodium, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, and other allergens. If an allergic reaction occurs during therapy with PIPRACIL, the antibiotic should be discontinued. The usual agents (antihistamines, pressor amines, and corticosteroids) should be readily available. SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN AND INTRAVENOUS CORTICOSTEROIDS AND AIRWAY MANAGEMENT INCLUDING INTUBATION SHOULD ALSO BE ADMINISTERED AS NECESSARY.

PRECAUTIONS: General. While PIPRACIL possesses the characteristic low toxicity of the penicillin group of antibiotics, periodic assessment of organ system functions including renal, hepatic, and hematopoietic during prolonged therapy is advisable. Bleeding manifestations have occurred in some patients receiving β-lactam antibiotics including piperacillin. These reactions have sometimes been associated with abnormalities of coagulation tests such as clotting time, platelet aggregation, and prothrombin time and are more likely to occur in patients with renal failure. If bleeding manifestations occur, the antibiotic should be discontinued and appropriate therapy instituted.

The possibility of the emergence of resistant organisms which might cause superinfections should be kept in mind, particularly during prolonged treatment. If this occurs, appropriate measures should be taken.

As with other penicillins, patients may experience neuromuscular excitability or convulsions if higher than recommended doses are given intravenously.

PIPRACIL is a monosodium compound containing 1.85 milliequivalents of Na^+ per gram. This should be considered when treating patients requiring restricted salt intake. Periodic electrolyte determinations should be made in patients with low potassium reserves, and the possibility of hypokalemia should be kept in mind with patients who have potentially low potassium reserves and who are receiving cytotoxic therapy or diuretics.

Antimicrobials used in high doses for short periods to treat gonorrhea may mask or delay the symptoms of incubating syphilis. Therefore, prior to treatment, patients with gonorrhea should also be evaluated for syphilis. Specimens for darkfield examination should be obtained from patients with any suspected primary lesion and serologic tests should be performed. In all cases where concomitant syphilis is suspected, monthly serological tests should be made for a minimum of four months.

As with other semisynthetic penicillins, PIPRACIL therapy has been associated with an increased incidence of fever and rash in cystic fibrosis patients.

Drug Interactions. The mixing of PIPRACIL with an aminoglycoside *in vitro* can result in substantial inactivation of the aminoglycosides.

Pregnancy—Pregnancy Category B. Although reproduction studies in mice and rats performed at doses up to four times the human dose have shown no evidence of impaired fertility or harm to the fetus, safety of PIPRACIL use in pregnant women has not been determined by adequate and well-controlled studies. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. It has been found to cross the placenta in rats.

Nursing Mothers. Caution should be exercised when PIPRACIL is administered to nursing mothers. It is excreted in low concentrations in milk.

Pediatric Use. Dosages for children under the age of 12 have not been established. The safety of PIPRACIL in neonates is not known. In dog neonates dilated renal tubules and peritubular hyalinization occurred following administration of PIPRACIL.

ADVERSE EFFECTS: PIPRACIL is generally well tolerated. The most common adverse reactions have been local in nature, following intravenous or intramuscular injection. The following adverse reactions may occur:

Local Reactions. Thrombophlebitis (4%), pain, erythema, and/or induration at the injection site (2%) and, less frequently, ecchymosis, deep vein thrombosis, hematomas.

Gastrointestinal. Diarrhea and loose stools (2%); less frequently, vomiting, nausea, increases in liver enzymes (LDH, SGOT, SGPT), hyperbilirubinemia, cholestatic hepatitis, bloody diarrhea, and, rarely, pseudomembranous colitis.

Hypersensitivity Reactions. Anaphylactoid Reactions (see WARNINGS). Rash (1%); less frequently, pruritus, vesicular eruptions, positive Coombs tests.

Renal. Elevations of creatinine or BUN and, rarely, interstitial nephritis.

Central Nervous System. Headache, dizziness, fatigue.

Hemic and Lymphatic. Reversible leukopenia, neutropenia, thrombocytopenia, and/or eosinophilia have been reported. As with other β-lactam antibiotics, reversible leukopenia (neutropenia) is more apt to occur in patients receiving prolonged therapy at high dosages or in association with drugs known to cause this reaction.

Serum Electrolytes. Individuals with liver disease, or individuals receiving cytotoxic therapy or diuretics, were reported rarely to demonstrate a decrease in serum potassium concentrations with high doses of piperacillin.

Skeletal. Rarely, prolonged muscle relaxation.

Other. Superinfection, including candidiasis.
Hemorrhagic manifestations.

Rev. 5/86

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Estimation of Oxygen Utilization by Dual Oximetry

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Total body oxygen utilization coefficient was estimated using continuous pulse and pulmonary artery oximetry (dual oximetry) in 17 patients with respiratory failure. Change in arterial and mixed venous oxygen saturations was induced by altering airway pressure. Continuous measurement of mixed venous oxygen saturation provided an accurate and linear estimate of oxygen utilization coefficient ($r = -0.92$), the true values being overestimated by 0.05 ± 0.06 (mean ± SD). Addition of pulse oximetry improved the correlation ($r = 0.93$) and decreased the difference between absolute values (0.02 ± 0.06). Oxygen utilization coefficient can be estimated reliably in an online fashion using pulmonary artery oximetry. However, the use of dual oximetry will further improve the estimate.

THE ULTIMATE GOAL of cardiopulmonary support is restoration and maintenance of adequate peripheral tissue oxygenation. However, little attention has been directed to monitoring of oxygen use. Most currently used indices of tissue oxygenation, such as mixed venous oxygen tension, arteriovenous oxygen content difference, and oxygen utilization coefficient, involve a time delay associated with blood sampling and, therefore, do not reveal rapid changes in the patient's physical status. Measurement of mixed venous blood oxyhemoglobin saturation ($S\bar{v}O_2$) with pulmonary artery oximetry recently was shown to correlate well with oxygen use coefficient (O_2UC).[1] The use of $S\bar{v}O_2$ alone to estimate O_2UC requires the assumption that the majority of change in blood oxygen content is reflected by oxyhemoglobin saturation and that arterial blood is fully saturated with oxygen. $S\bar{v}O_2$ is inversely related to O_2UC and represents the fractional amount of oxyhemoglobin that remains after blood has traversed the tissues.

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Assumption of 100% saturation of arterial blood oxyhemoglobin is unnecessary if pulse oximetry is applied. This investigation determines the accuracy with which O_2UC can be estimated using mixed venous oximetry and an oxygen extraction index (O_2EI) obtained by simultaneous pulse and pulmonary artery oximetry (dual oximetry).

Patients and Methods

The study protocol was approved by the Human Subjects Review Committee of the Ohio State University. Informed consent was obtained from the families of 17 patients who were treated in the Surgical Intensive Care Unit. All patients had acute lung injury that responded to alteration of continuous positive airway pressure (CPAP) with a change in SaO_2. No patient was actively bleeding during the study, nor was any patient receiving blood transfusion or rapid fluid infusions. Variables reflecting the cardiopulmonary function of the patients at the time of data collection are summarized in Table 1.

All patients' tracheas had been intubated before the study and they were receiving at least 5 cmH_2O expiratory airway pressure, either with a ventilator or with a venturi powered CPAP apparatus, as part of their treatment. Patients had indwelling arterial catheters for blood sampling and for measurement of systemic blood pressure. A pulmonary artery catheter equipped with a fiberoptic cable (American Edwards Laboratories, Santa Ana, CA) was inserted and connected to a mixed venous saturation monitor (Sat-1, American Edwards Laboratories), which also was used for thermodilution cardiac output measurements. The saturation monitor was calibrated *in vivo* using a technique suggested by the manu-

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TABLE 1. *Variables Reflecting Cardiorespiratory Function in 17 Patients with Respiratory Failure*

Variable	Mean ± SD	Range
CPAP (cmH_2O)	14 ± 5	5–20
F_IO_2	0.38 ± 0.08	0.30–0.60
PaO_2 (mmHg)	78 ± 18	54–114
$PaCO_2$ (mmHg)	37 ± 6	30–50
Qs/Qt (%)	24 ± 10	8–45
pHa	7.42 ± 0.05	7.30–7.52
Cardiac output (L/min)	6.9 ± 2.4	2.7–11.4
$C(a - \bar{v})O_2$ (mL/dL)	4.0 ± 1.3	2.4–6.8
$S\bar{v}O_2$ (%)	69 ± 9	56–83

facturer. A pulse oximeter probe (Nellcor, Inc., Hayward, CA) was attached to the patient's finger.

After instrumentation, CPAP was changed in steps of 2.5 cmH_2O to produce a change in arterial and mixed venous blood oxygen content. Inspired oxygen concentration initially was adjusted to produce arterial blood oxygen saturation between 94 and 96% and was not changed during data collection. After 5 minutes of equilibration at each level of CPAP, cardiac output, heart rate, respiratory rate, pulmonary artery temperature, and oximeter readings were obtained. Immediately after recording the oximetric saturations, arterial and mixed venous blood were sampled. Progressive change in CPAP in a given direction was discontinued if any of the following conditions were met: an SaO_2 less than 90% or greater than 99%, an increase in $PaCO_2$ by 15%, a spontaneous respiratory rate greater than 35 cycles/min, or a decrease in left ventricular stroke volume by 15%. Arterial and mixed venous blood samples were analyzed for blood gases and pH within 5 minutes of sampling. Oxygen saturations and oxygen contents (CaO_2, $C\bar{v}O_2$) were calculated using a computer program.[2] Then, oxygen utilization coefficient was calculated using the formula:

$$O_2UC = CaO_2 - C\bar{v}O_2/CaO_2$$

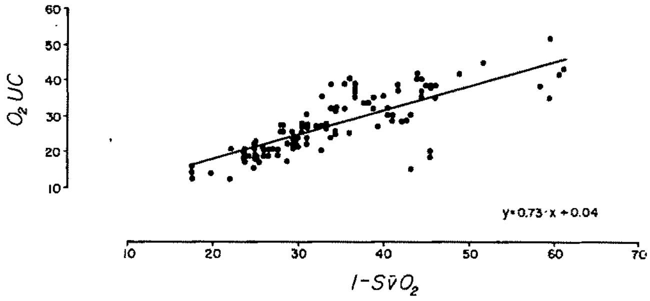

FIG. 1. Relationship between oxygen utilization coefficient (O_2UC) and 1-$S\bar{v}O_2$ in 17 patients with respiratory failure.

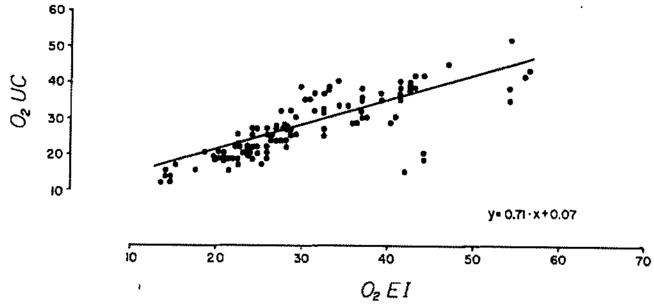

FIG. 2. Relationship between oxygen utilization coefficient (O_2UC) and oxygen extraction index (O_2EI) in 17 patients with respiratory failure.

Oxygen extraction index was calculated from arterial and mixed venous oxygen saturations obtained by dual oximetry using the formula:

$$O_2EI = SaO_2 - S\bar{v}O_2/SaO_2$$

For comparison of O_2EI and SvO_2 as estimates of O_2UC, mixed venous oximetry data were transformed by calculating $1 - S\bar{v}O_2$.

Statistical Analysis

Pearson's correlation coefficients were calculated using a randomly selected value obtained from each patient to assess the intersubject correlations between O_2UC, O_2EI, and $S\bar{v}O_2$. A repeated measures linear regression analysis was used to test how well the relationships between O_2UC and its estimates fit to a linear model.[3] This procedure permits the use of the multiple observations collected for each patient. The logarithm of the distribution function (LogL) was used to assess the relative goodness of fit of the linear relationship between the variables. The larger the value of LogL, the better the fit.[4] Homogeneity of variances was assessed using the Bartlett test.

Results

The study group consisted of 11 men and six women with a mean age of 57 ± 15 years (mean ± SD). Eight patients had acute respiratory failure associated with abdominal sepsis, one had fat embolism syndrome, one had pulmonary contusion, and seven patients had postoperative pulmonary failure without apparent systemic cause. Seven levels of CPAP were studied in 11 patients, six levels in two, five levels in three, and nine levels in one patient, for a total of 113 data points.

The data covered an SaO_2 range from 89 to 99% (95 ± 2%; mean ± SD) and an O_2UC range from 0.13 to 0.54 (0.29 ± 0.09). Correlation between O_2UC and O_2EI was slightly higher ($r = 0.93$; $p < 0.0001$) than that between O_2UC and $1 - S\bar{v}O_2$ ($r = 0.92$; $p < 0.0001$). Both O_2EI (LogL = 293) and $1 - S\bar{v}O_2$ (LogL = 285) fit well to a linear relationship with O_2UC in the repeated measures linear regression analysis (Figs. 1 and 2). The differences between O_2EI and O_2UC averaged 0.02 ±

0.06, while the difference between 1 − $S\bar{v}O_2$ and O_2UC was 0.05 ± 0.06. The difference between 1 − $S\bar{v}O_2$ and O_2EI averaged 0.04 ± 0.02 and ranged from 0.01 to 0.09. It correlated inversely with SaO_2 ($r = -0.90$; $p < 0.0001$). There was a fair correlation between O_2UC and cardiac output ($r = -0.55$; $p < 0.05$) and between O_2UC and tissue oxygen delivery ($r = -0.64$; $p < 0.01$), but no significant correlation between O_2UC and PaO_2, CaO_2, or oxygen consumption.

Discussion

This investigation was designed to determine whether continuous measurement of arterial and mixed venous oxygen saturations would be useful in estimating total body oxygen use. We found that mixed venous oximetry alone provided a clinically useful, linear estimate of O_2UC. The addition of pulse oximetry further improved the accuracy of the estimate.

Since methods that directly measure tissue oxygen dynamics are unavailable for clinical use, changes in oxygen balance must be evaluated from calculations of total body oxygen use. The ratio of oxygen consumption and oxygen delivery, the oxygen utilization coefficient, currently is the most accurate method available for routine assessment of tissue oxygen balance. Alterations in O_2UC reflect changes in both oxygen delivery and oxygen consumption. Therefore, measurement of O_2UC cannot be replaced by separate assessment of oxygen delivery, oxygen consumption, or their components. This fact is reflected in the results of the current study: O_2UC did not correlate well with oxygen delivery or oxygen consumption. Similar results were obtained by Nelson for SvO_2, an estimate of O_2UC.[1]

If arterial blood oxygen content remains constant, change in O_2UC is reflected directly in mixed venous oxygen content. Since oxygen content is determined primarily by oxyhemoglobin saturation, changes in O_2UC also will be reflected by alteration in SvO_2. Nelson found O_2UC to be the variable with which oximetrically measured SvO_2 is related most consistently ($r = -0.92$).[1] Our results show a similar high correlation between O_2UC and $S\bar{v}O_2$ ($r = -0.92$). These results indicate that $S\bar{v}O_2$ can be used to estimate peripheral oxygen use. In addition, it can be measured continuously without blood sampling.

Assumption of constant and complete saturation of arterial blood oxyhemoglobin results in progressive overestimation of O_2UC from SvO_2 as SaO_2 decreases. Therefore, accuracy of estimation of O_2UC will be increased by measuring arterial blood oxyhemoglobin saturation with pulse oximetry, particularly in patients with low and variable SaO_2. In this study, the variation in O_2UC explained by the estimate (r^2) remained similar (84% *vs.* 87%) when pulse oximetry was added, but the difference in absolute values decreased. Use of measured, rather than calculated, saturations could have improved our results slightly. However, the large explained variation (87%) indicates a strong likelihood that calculated saturations were fairly accurate. Certainly they are of greater clinical utility.

Even though pulmonary artery oximetry alone can be used to estimate O_2UC with a small and clinically acceptable error, the noninvasive nature of pulse oximetry warrants the use of dual oximetry for monitoring peripheral oxygen use in most patients who require pulmonary artery oximetry.

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Magnetic Resonance Imaging for Detection of Arterial and Venous Occlusion in Canine Muscle Flaps and Bowel Segments

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Magnetic resonance imaging (MRI) was performed on 16 muscle flaps and eight jejunal segments in dogs to assess its usefulness in detecting vascular occlusion. Arterial or venous occlusion was carried out in 11 muscles and six bowel segments, with the remaining sham flaps serving as controls. Imaging was performed over 2 hours using a spin echo pulse sequence with T2 weighting. Arterial occlusions in muscles resulted in T2 values 15–30% higher than controls, while venous occlusion produced T2 values 55–75% higher than controls. Differences became significant ($p < 0.05$) at 10 minutes after venous occlusion and at 35 minutes after arterial occlusion. Differences between occluded and control bowel segments, although demonstrating a similar trend, failed to reach statistical significance in this preliminary study. The authors conclude that magnetic resonance imaging may be a valuable method for early detection of venous and arterial occlusion in muscle flaps. Further study may also demonstrate this technique to be useful in the diagnosis of ischemic bowel.

FREE TRANSFER OF myocutaneous flaps and jejunal grafts is an integral component in reconstruction of defects caused by trauma, infection, radiation, congenital defects, and radical tumor surgery.[1] The literature reports a failure rate of 5–20% due to thrombosis,[2–4] with successful reexploration in only 50%.[5] This may be due to irreversible cellular damage occurring after approximately 12 hours of ischemia that is referred to as the "no reflow" phenomenon.[4,6–10] No single method of detecting vascular occlusion has gained widespread acceptance, and clinicians rely primarily on visual changes in graft perfusion to assess anastomotic patency. A rapid noninvasive method of confirming a suspected thrombosis is needed.[11]

Magnetic resonance imaging (MRI) measures changes in total water and water distribution in tissues.[12,13] Studies have demonstrated its sensitivity in detecting vascular occlusion in myocardium,[14–17] striated muscle,[11] and renal parenchyma.[18,19]

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This study was undertaken to evaluate MRI as a means of detecting arterial and venous occlusion in muscle flaps and jejunal grafts.

Materials and Methods

Experimental Preparation

Five mongrel dogs weighing over 30 pounds were anesthetized using sodium pentobarbital (35 mg/kg) and allowed to breathe spontaneously through an endotracheal tube. Gracilis and rectus femoris flaps were developed with isolation of the major vascular pedicle. Two dogs underwent additional celiotomy through a vertical midline incision for isolation of jejunal segments measuring 6–8 cm. A single vascular arcade was isolated and the segments were divided from the adjacent bowel after visual confirmation of adequate perfusion and then placed on the abdominal wall. Baseline imaging was performed on all muscle flaps and bowel loops. Arterial or venous occlusion was carried out in a random fashion, and imaging was repeated at approximate 10–20 minute intervals over 130 minutes. Investigators performing the actual MRI measurements were blinded to the type of occlusion performed. All animals were killed at the end of the study.

Magnetic Resonance Imaging

Magnetic resonance imaging was performed using a Phillips Gyroscan (Phillips Medical Services, Eindhoven, The Netherlands), a 1.5 Tesla superconducting magnet operating at 0.5 Tesla (proton magnetic resonance 21.3 MHz). A spin echo (SE) pulse sequence was used with echo times (TE) of 30 and 60 msec, and repetition time (TR) of 2000 msec. A multislice acquisition

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TABLE 1. *T2* Versus *Time for Control and Occluded Grafts**

Time (Min)	Control (±SD)	Artery (±SD)	Vein (±SD)
0	36.8 ± 4.1	42.2 ± 5.9	38.1 ± 3.0
10	34.9 ± 2.8	43.5 ± 8.6	54.0 ± 10.6
25	38.1 ± 6.9	43.8 ± 7.0	63.6 ± 8.1
50	35.2 ± 3.2	43.5 ± 7.4	59.4 ± 6.6
65	38.3 ± 5.2	46.3 ± 7.0	65.2 ± 4.5
75	39.0 ± 4.0	49.1 ± 6.4	68.8 ± 6.2
105	39.0 ± 3.9	47.2 ± 7.1	65.5 ± 11.8
120	40.8 ± 4.9	47.9 ± 7.7	67.2 ± 7.3
130	40.0 ± 5.7	51.4 ± 9.7	63.1 ± 5.4

* Relaxation times (T2) of control and occluded muscle flaps over time.

TABLE 2. *T2* Versus *Time for Control and Occluded Grafts**

Time (Min)	Control (±SD)	Artery (±SD)	Vein (±SD)
0	52.5 ± 3.2	51.7 ± 9.2	59.6 ± 7.9
10	66.2 ± 8.2	76.3 ± 6.3	62.4 ± 7.3
25	73.2 ± 6.4	75.8 ± 7.9	77.9 ± 8.1
50	67.2 ± 4.4	82.5 ± 10.3	87.2 ± 7.5
75	73.8 ± 5.0	77.5 ± 8.4	97.3 ± 10.7
90	68.0 ± 4.7	70.6 ± 2.7	91.6 ± 7.4
120	69.1 ± 3.2	83.2 ± 8.6	91.5 ± 2.3
130	66.1 ± 5.4	79.6 ± 8.6	87.8 ± 7.2

* Relaxation times (T2) of control and occluded bowel segments over time.

was used with a 5-mm slice thickness at 10-mm intervals. A 256 × 256 matrix was used on the first dog and a 128 × 256 matrix for the succeeding dogs. All images were acquired with the body coil and with two averages. At least three intensity measurements from two echoes were obtained from each muscle flap and bowel segment. T2 values were calculated using the equation:

$$T2 = (t_2 - t_1)/\ln(I_{t_1}/I_{t_2})$$

where t_1 and t_2 represent spin echo times (TE) and I_{t_1} and I_{t_2} represent peak signal intensity at time t.

Statistics

T2 values from all similarly developed flaps were averaged and a standard deviation calculated. Comparison between groups was made with the Student's two-tail t-test. Differences were considered significant if $p < 0.05$.

Results

T2 relaxation times ± SD for control and occluded muscle flaps are shown in Table 1. Measurements taken at time 0 represent baseline values prior to vascular ligation. Average T2 for control muscles over 130 minutes was 38.0 ± 2.0. Arterial ligation produced a 15–30% increase in mean T2 values above controls. This difference was apparent by 10 minutes after occlusion but did not reach statistical significance ($p < 0.05$) until 35 minutes after ligation. Average T2 after 35 minutes was 47.6 ± 2.7. Results of venous occlusion in muscle flaps became significant ($p < 0.05$) by 10 minutes due to markedly elevated T2s. These ranged 55–75% higher than controls. Average T2 after 10 minutes was 63.4 ± 4.7.

Results of arterial and venous ligation in isolated bowel loops are shown in Table 2. Average T2 for controls over 130 minutes was 67.0 ± 6.6. T2 values for arterial and venous occlusion in bowel averaged 78.0 ± 4.3 and 91.1 ± 4.0, respectively. Although a trend was definitely suggested, these data failed to reach statistical significance in this pilot study.

Comparisons of control and occluded muscle flaps and bowel segments are depicted in Figures 1 and 2.

Discussion

Free transfers of muscle for coverage of soft tissue defects, and of jejunum for cervical esophageal replacement are important new advances in plastic surgical technique practiced in most major centers.[1,2,6,20] These procedures are complicated by an overall 5–20% failure rate due to thrombosis,[2–4] with a successful reexploration rate of only 50%.[5] Thrombosis appears to occur within 48 hours of anastomosis[6,9] and revascularization must be performed within 12 hours of occlusion. Delay results in the "no reflow" phenomenon, probably due to irreversible cellular damage.[4,6–10] This may be reflected by decreased ATP and cAMP and increased levels of lactate, as seen in dying skin flaps.[21]

No single technique for detecting early vascular occlusion in flaps has attained widespread acceptance, as

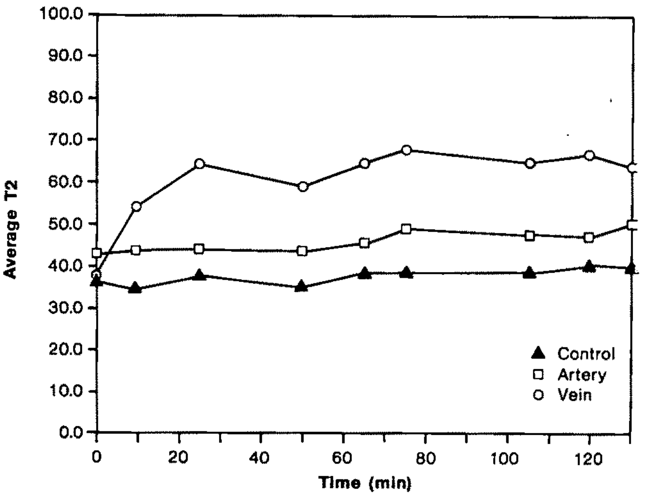

FIG. 1. T2 *versus* time for muscle flaps. Comparison of relaxation times in control and occluded muscle flaps over time. T2 values expressed in msec. Measurements at time 0 represent preligation baseline T2s.

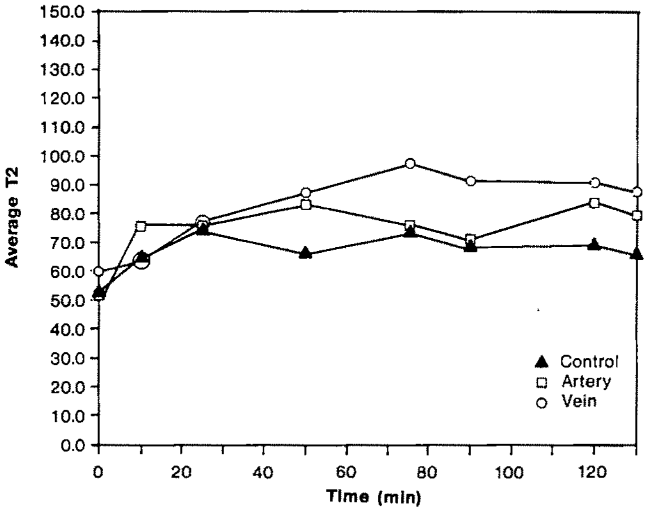

FIG. 2. T2 *versus* time for bowel segments. Comparison of relaxation times in control and occluded bowel segments over time. T2 values expressed in msec. Measurements at time 0 represent preligation baseline T2s.

evidenced by the abundance of publications on this subject. It is generally agreed that the method should be safe, noninvasive, accurate, and simple.[3,9,10,22-25] In addition, the problem of monitoring buried flaps must be addressed.[4,23]

Existing techniques to assess flap viability are based on physiologic or blood flow measurements, yielding either qualitative or quantitative results.

Qualitative methods all measure flap blood flow, either at the pedicle or in the muscle itself. Staining with fluorescein or sulfan blue is unreliable and nonrepeatable.[23,25-27] Stereomicroscopy of surface vessels is impractical and highly subjective.[28] Clearance of radioisotopes is inconsistent, nonrepeatable, and requires radiation exposure.[6,9,23,26] Doppler ultrasound, although promising in some studies, demands precise probe placement directly on the vessels and is not useful in end-to-side anastomoses.[6,9,23,25,26,29,30]

Quantitative methods may measure blood flow or physiologic parameters to assess flap viability. The physiologically oriented techniques include transcutaneous O_2 and CO_2 sensors, surface thermometers, pH monitors, and electrical impulse detectors. Transcutaneous gas sensors have produced inconsistent results and can be associated with burns to the skin. In addition, anesthetic gases may interfere with transcutaneous O_2 readings.[5,6,8,26,31-33] Surface thermometry responds too slowly to changes in perfusion to be clinically useful.[6,23,25] pH probe studies have been encouraging, but results may be misleading due to systemic perfusion alterations.[26,34] Evoked M waves are sensitive indicators of muscle contractility according to one study, but the technique is complex and cumbersome.[4]

Quantitative blood flow measurements are the most accurate methods of flap monitoring. These include reflection photoplethysmography, laser Doppler flowmetry, and electromagnetic flowmetry. Photoplethysmography is only useful in flaps with a skin surface and cannot be used for denuded or buried grafts.[6,9,23,25,26,35] Doppler and electromagnetic flowmeters require precise placement of probes directly on the vascular pedicle and interpretation of complex wave forms.[6,23,25,30,36-38]

All of the methods mentioned have advantages and disadvantages. Shortcomings include inability to monitor buried flaps and difficulty distinguishing arterial from venous occlusion. A method capable of detecting occlusion under these circumstances would be most useful.

Magnetic resonance imaging is a relatively new technique undergoing vigorous investigation in a variety of settings.[11-13,15-19,39] MRI is a form of spectroscopy based on magnetic and spin properties of nuclides. When placed in a magnetic field and pulsed with a specific radiofrequency, these nuclides absorb energy. When the pulse is terminated, the nuclides relax to their ground state. The characteristic relaxation is defined as the average time required for a nuclide to reach its ground state.[11,12,13,40] Hydrogen magnetic resonance has been used extensively to study the "state" of water in living tissues. These molecules exist in bound and unbound fractions, which characteristically relax at different rates, and their ratio is influenced by protein and ion concentrations.[17-19] This technique can therefore be used to study tissue physiology at the molecular level. Several investigators have demonstrated increased relaxation times of hydrogen protons in infarcted skeletal muscle in rats,[11] and infarcted myocardium in dogs that paralleled increases in total water content.[14-17] Recently, MRI methods have been used to detect arterial and venous occlusion in rabbit kidneys.[18,19]

Our study demonstrates an unequivocal increase in relaxation time (T2) with venous occlusion of both muscle and bowel grafts. In contrast, arterial occlusion produced only slight increases in T2. Ischemia, due to arterial or venous occlusion, is known to result in loss of cell membrane integrity with resultant increase in intracellular water and shift in ion concentrations, which produce alterations in the ratio of bound to free water.[7,15-19,41] Venous occlusion also results in a marked increase in the total water content. The latter mechanism is probably responsible for the larger increase in T2 noted in our venous as compared to our arterial occlusions. Intracellular water shifts probably contribute to the increased T2 in our venous occlusions and are most likely responsible for the slight increase in T2 noted in our arterial occlusions. Interestingly, our bowel experiments yielded control values for T2 significantly higher than those in muscle (67.0 *vs.* 38.0 msec). This may reflect an inherent difference in relaxation time of bowel, or may be due to ischemia induced by ligation of adjacent vascular collateral arcades.

This study confirms the ability of MRI to detect venous occlusion. Changes in T2 during arterial occlusion, however, may be too subtle for clinical application. Addition of paramagnetic contrast agents may solve this dilemma. These compounds decrease the relaxation time of water in tissues.[13,17,19] Experiments in rabbit kidneys with infusions of manganese, a paramagnetic ion, have demonstrated no change in T2 values of arterially occluded kidneys, but a significant decrease in T2s of normally perfused kidneys.[19] Use of these paramagnetic ions may enhance detection of arterial occlusion in grafts. Further research in this area is needed.

Acknowledgment

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A Prospective Study of Vein Patch Angioplasty During Carotid Endarterectomy

Three-year Results for 801 Patients and 917 Operations

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From 1983 through 1985, 801 consecutive patients (mean age: 66 years) underwent 917 primary carotid endarterectomies at the Cleveland Clinic. Conventional arteriotomy closure was performed during 483 operations, while patch angioplasty using a distal segment of saphenous vein was employed in 434. Preoperative risk factors, surgical management, and antiplatelet therapy were equivalent in the vein patch (VP) and nonpatch (NP) groups. Early results were evaluated by intravenous angiography (DSA) in 715 patients (89%), and 332 reconstructions (36%) have been reassessed by objective imaging during a mean follow-up interval of 21 months. Ischemic strokes occurred after 18 (1.9%) of the 917 procedures (0.7% VP, 3.1% NP; $p = 0.0084$), and symptomatic ($N = 9$) or unsuspected ($N = 8$) thrombosis of the internal carotid artery was confirmed by neck exploration or routine DSA after 1.9% of all operations (0.5% VP, 3.1% NP; $p = 0.0027$). Only ten patients (1.2%) have required reoperations for severe recurrent lesions, but the cumulative 3-year incidence of new defects ($\geq$30% stenosis) documented by objective studies in the VP and NP groups was 9% and 31%, respectively ($p = 0.0066$). These results strongly suggest that VP angioplasty enhances the safety and durability of carotid endarterectomy.

CONTROVERSY CONCERNING CEREBROVASCULAR surgery was abruptly intensified in 1985, when the EC/IC Bypass Study Group concluded that medical therapy was as effective as middle cerebral revascularization in the treatment of intracranial arterial disease.[1] In response to this investigation as well as to the fact that carotid endarterectomy has become one of the most common vascular procedures performed in the United States, influential neurologists have suggested that even extracranial reconstruction may no longer be justified outside the framework of prospectively randomized clinical trials.[2-4] Without exception, these criticisms were supported by the high operative stroke and/or death rates reported several years ago by Easton and Sherman[5] in southern Illinois (21%), and more recently by Brott et al.[6,7] in Cincinnati (6.5–9.5%).

Excessive surgical complications obviously have a legitimate influence on medical opinion. For example, Chambers and Norris[4] calculated in 1984 that asymptomatic carotid bifurcation lesions should be corrected only if a subset of patients could be identified in which the annual incidence of stroke without operation was 5% or more. The same authors found in 1986 that the spontaneous risk of severe stenosis (>75% by Doppler ultrasonography) actually exceeded this figure (5.5%), yet they again discouraged elective intervention because four (13%) of the 30 patients in their series who underwent carotid endarterectomy had perioperative strokes.[8] Countless other studies have demonstrated that the composite morbidity and mortality of carotid endarterectomy is less than 3% at many centers, but it is inevitable that the merit of this operation will be open to speculation until its safety is universal.

Dependable technical results are essential to the success of carotid endarterectomy. The bifurcation must be widely patent and relatively resistant to platelet aggregation in order to prevent thrombosis or microembolization, but in each of these respects, routine arteriotomy closure occasionally may be inadequate. Turnipseed et al.[9] and Ortega et al.[10] have documented postoperative internal carotid occlusions in 3–5% of patients evaluated by noninvasive methods, whereas others using intraoperative ultrasound have consistently discovered residual intraluminal defects in 7–8% of their series.[11-13] Early thrombosis has been recognized after approximately 2% of the carotid endarterectomies performed at the Cleveland Clinic, and neurologic deficits occurred with fewer than half of these events.[14,15] In 1983, however, we ini-

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tiated a prospective study of vein patch (VP) angioplasty in an attempt to eliminate, if possible, all serious complications of an operation for which perfection appears to be the only acceptable standard. This report is a summary of the first 3 years of our experience with carotid patching.

Materials and Methods

Patch angioplasty previously had been performed on a selective basis in approximately 7% of patients who required carotid endarterectomy at the Cleveland Clinic, but one of us (N.R.H.) decided early in 1983 to apply a routine patch of saphenous vein harvested from the ankle to determine whether this precaution might influence the perioperative complication rate and/or the incidence of recurrent stenosis. Excluding late reoperations and any procedures that were limited to the external carotid artery, 801 patients underwent a total of 917 conventional bifurcation endarterectomies within the subsequent 32 months of the investigation. The remaining authors continued to patch selectively during this time, but Figure 1 illustrates that their preference for primary closure declined throughout the study period. In summary, there were 233 patients (273 operations) in the routine patch group, whereas selective patching was used in another 135 (161 operations). Only 14 entrants (1.7%) received bilateral reconstructions with a patch on one side but not on the other; demographic and survival information for this small subset was included with the non-patched (NP) group (Tables 1 and 4, Fig. 2), but the cumulative neurologic data for these 14 patients were calculated in the VP group as well (Fig. 3).

Patient Information

The VP and NP groups contained 368 and 433 patients, respectively. As indicated by the comparisons in Table 1, these two cohorts had similar clinical features.

Sex and Age

There were 563 men (70%) and 238 women (30%) in the entire series. The men ranged in age from 40 to 84 years (mean: 65 years), whereas the women were 47–87 years of age (mean: 67 years).

Surgical Indications

Unilateral carotid endarterectomy was performed in 685 patients, but 116 (14%) required bilateral procedures during the study period. Previous neurologic events had occurred in 393 patients (49%), including 141 (18%) with completed strokes followed by good functional recovery, 123 (15%) with cortical transient ischemic attacks (TIA), and 129 (16%) with amaurosis

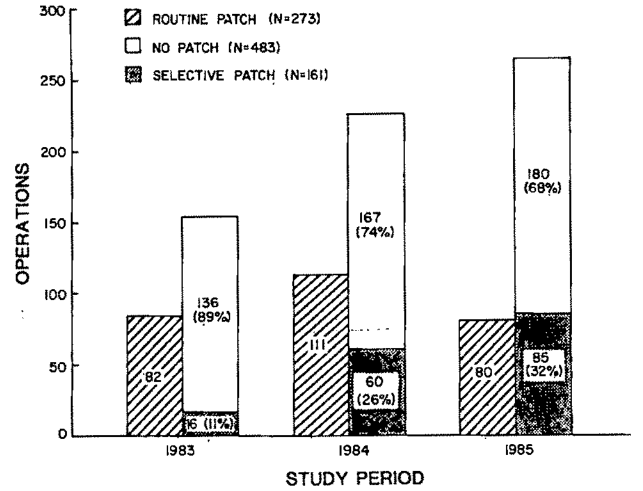

FIG. 1. Composition of the routine and selective patch groups in this series.

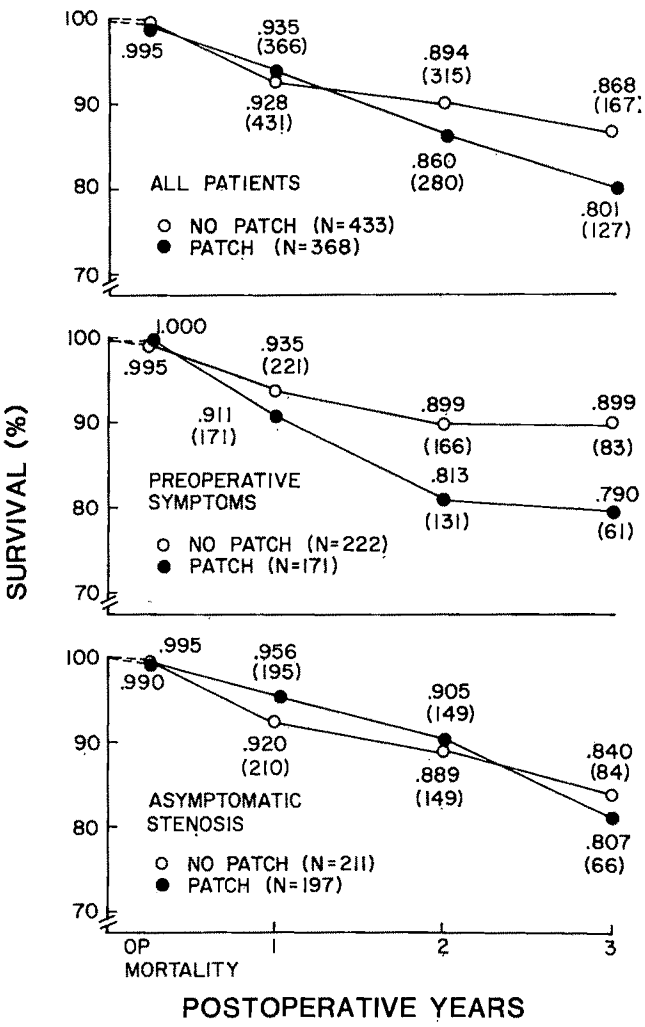

FIG. 2. Three-year life table survival according to the preoperative neurologic status. The number of eligible patients at each interval is enclosed in parentheses.

TABLE 1. *Clinical Features for the 801 Patients in the Study Group*

Clinical Features	No Patch No.	No Patch %	Patch No.	Patch %
Patients	433	100	368	100
Sex				
Men	319	74	244	66
Women	114	26	124	34
Age				
Range	45–85		40–87	
Mean	66		65	
Procedures				
Unilateral	369	85	316	86
Bilateral	64	15	52	14
Surgical indications				
Symptomatic disease	222	51	171	46
Prior stroke	88	20	53	14
Transient ischemia	62	14	61	17
Amaurosis fugax	72	17	57	15
Asymptomatic stenosis	211	49	197	54
Risk factors				
Hypertension	300	69	254	69
Diabetes mellitus	90	21	70	19
Antiplatelet therapy				
Preoperative	249	58	194	53
Postoperative	376	87	288	78

fugax or microembolic retinal infarcts. The remaining 408 patients (51%) had asymptomatic carotid stenosis (N = 385, 48%) or subtotal lesions associated with nonspecific vertebrobasilar symptoms (N = 23, 3%).

Risk Factors and Antiplatelet Therapy

A total of 554 patients (69%) either had hypertension (BP ≥ 180/90 mmHg) or already required antihypertensive management. Diabetes mellitus under treatment with insulin or oral hypoglycemic agents was present in 160 patients (20%). Serum cholesterol values were available for 696 entrants (87%) and ranged from 91 to 995 mg/dL, with a mean of 245 mg/dL (NP, 240 mg/dL; VP, 252 mg/dL). Triglyceride levels were obtained for 206 patients (26%) and ranged from 35 to 4400 mg/dL with a median of 245 mg/dL (NP, 252 mg/dL; VP, 238 mg/dL).

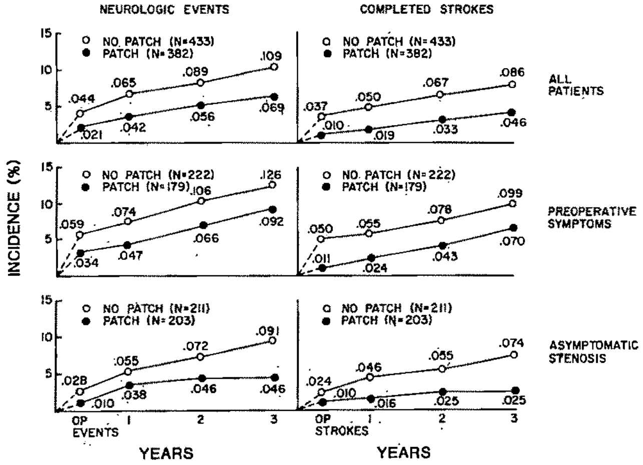

FIG. 3. The cumulative incidence of all ipsilateral neurologic events (left) and completed strokes (right) within the perioperative and late study periods.

Antiplatelet agents (aspirin and/or dipyridamole) were prescribed before surgery for 443 patients (56%), whereas 664 (83%) complied with antiplatelet therapy during the early postoperative course as well as the late follow-up interval. Another 52 patients (6%) received coumadin before their operations, and 27 (3%) have remained on formal anticoagulation after carotid endarterectomy.

Surgical Considerations

All 917 procedures in this series were conducted using general anesthesia, routine carotid shunting, and systemic heparinization that was at least partially reversed with protamine sulfate at the conclusion of each operation. The saphenous patch usually was obtained at the medial malleolus, but it was removed from the upper calf whenever the arterial circulation appeared inadequate to heal a harvesting incision near the foot. There were no wound complications with this approach, and the loss of a segment of vein close to the ankle did not interfere with subsequent *in situ* saphenous grafts in the few patients who already were scheduled for elective lower extremity revascularization at the time their carotid disease was discovered.

The carotid arteriotomy was repaired primarily during 483 operations, whereas patch angioplasty was performed in 434. Additional surgical considerations were comparable in both groups (Table 2).

Associated Procedures

Only nine (1%) of the 917 operations were necessary to correct incidental carotid lesions in patients who originally were evaluated because of other manifestations of peripheral vascular disease. Another 161 procedures (18%), however, were either staged (N = 53, 6%) or combined (N = 108, 12%) with open heart surgery in cardiac patients. Altogether, 122 (26%) of the 464 endarterectomies for asymptomatic carotid stenosis were done in conjunction with myocardial revascularization.

Angiographic Status

Preoperative angiograms demonstrated severe (≥70%) stenosis of the ipsilateral common carotid or internal carotid artery preceding 724 operations (79%). Severe stenosis or occlusion of the contralateral internal carotid was present at the time of 215 procedures (23%), but the incidence of advanced contralateral carotid disease was similar in the VP (25%) and NP cohorts (22%).

TABLE 2. *Surgical Considerations for the 917 Carotid Endarterectomies Performed During the Study Period*

Surgical considerations	No Patch No.	No Patch %	Patch No.	Patch %
Operations	483	100	434	100
Associated Cardiac procedures				
Staged	29	6	24	6
Simultaneous	53	11	55	13
Ipsilateral Carotid stenosis				
<50%	47	10	28	6
50–69%	63	13	55	13
70–89%	198	41	144	33
≥90%	175	36	207	48
Contralateral Carotid stenosis				
<50%	324	67	279	64
50–69%	53	11	46	11
70–89%	41	8	26	6
≥90%	12	3	20	5
Occlusion	53	11	63	14

Postoperative Assessment

Early technical results were documented by intravenous digital subtraction angiography (DSA) during the same hospital admission in 715 (89%) of the 801 patients. Although 14 operative survivors (1.8%) have been lost, late clinical results were available for the remainder of the series during a maximum follow-up interval of 40 months (mean: 21 months). Within this period, 332 (36%) of the 917 carotid endarterectomies were reassessed by DSA (N = 290, 87%) or Doppler ultrasonography (N = 42, 13%). Long-term objective imaging was obtained for 43% of the VP group and for 30% of the NP group.

Statistical Analysis

Paired data were compared using Fisher's exact test. Life table calculations were performed according to Cutler and Ederer[16] and were evaluated with the method described by Lee and Desu.[17]

Results

Early Results

A summary of perioperative complications for all 917 operations in the series is presented in Table 3.

Operative mortality. Although 14 patients (1.7%) died as the result of cardiac or other peripheral vascular procedures that were performed within the first month after carotid endarterectomy, only four fatal complications (0.5%) were related directly to extracranial reconstruction. Two of these patients (1 VP, 1 NP) had delayed cerebral hemorrhage and another sustained a myocardial infarction following endarterectomy alone. The fourth patient experienced a brainstem stroke during simultaneous coronary and carotid revascularization and eventually developed irreversible multisystem failure. Nevertheless, early mortality was identical irrespective of whether patch angioplasty had been employed.

Ischemic neurologic deficits. Seven transient neurologic deficits (0.8%) were evenly distributed (4 VP, 0.9%; 3 NP, 0.6%) and disappeared completely within hours after recovery from general anesthesia. Ischemic strokes with persistent functional impairment occurred in conjunction with 18 operations (1.9%), and all involved the ipsilateral cerebral hemisphere. The difference between early stroke rates in the VP (0.7%) and NP groups (3.1%) was statistically significant (p = 0.0084).

Internal carotid occlusion. Postendarterectomy thrombosis of the internal carotid artery was documented by immediate neck exploration or angiography in nine of the 15 patients who experienced perioperative strokes in the NP cohort, and all nine of these patients underwent urgent thrombectomy with secondary patch angioplasty. In comparison, symptomatic thrombosis did not occur in the primary patch group (p = 0.0041). Eight other patients (1%) were found to have asymptomatic internal carotid occlusions during routine postoperative DSA studies performed before their discharge from the hospital (2 VP, 0.5%; 6 NP, 1.2%). Thus, a total of 15 early occlusions (3.1%) were associated with standard arteriotomy closure, whereas only two clinically silent events (0.5%) were identified in the patch group (p = 0.0027).

TABLE 3. *Operative Complications for the Complete Series of 917 Carotid Endarterectomies*

Operative Complications	No Patch (N = 483) No.	No Patch (N = 483) %	Patch (N = 434) No.	Patch (N = 434) %
Related mortality	2	0.5	2	0.5
Neurologic events	19	3.9	8	1.8
Transient ischemia	3	0.6	4	0.9
Completed stroke	15	3.1	3	0.7
Hemorrhagic infarction	1	0.2	1	0.2
Internal carotid thrombosis	15	3.1	2	0.5
Symptomatic	9	1.9	0	—
Asymptomatic	6	1.2	2	0.5
Miscellaneous				
Cervical hematoma	7	1.4	7	1.6
Patch disruption	—	—	3	0.7

TABLE 4. *Selected Comparisons Concerning Perioperative Ischemic Stroke and Internal Carotid Thrombosis Among the 801 Patients Studied*

		No Patch (N = 433)		Patch (N = 368)	
Patient Comparisons	N	No.	%	No.	%
Ischemic stroke					
Sex					
Men	563	10/319	3.1	2/244	0.8
Women	238	5/114	4.4	1/124	0.8
Neurologic status					
Asymptomatic stenosis	408	4/211	1.9	1/197	0.5
Previous TIA*	252	7/134	5.2	1/118	0.8
Prior stroke	141	4/88	4.5	1/53	1.9
Contralateral carotid					
Patent	685	12/380	3.2	1/305	0.3
Occluded	116	3/53	5.7	2/63	3.2
Perioperative thrombosis					
Sex					
Men	563	13/319	4.1	1/244	0.4
Women	238	2/114	1.8	1/124	0.8
Preoperative Antiplatelet therapy					
Yes	443	8/249	3.2	1/194	0.5
No	358	7/184	3.8	1/174	0.6

* TIA = transient ischemic attack or amaurosis fugax.

Patch disruption. Semielective evacuation of simple cervical hematomas was necessary after 14 (1.5%) of the 917 procedures (7 VP, 1.6%; 7 NP, 1.4%). Another three patients (0.7%) in the patch group, however, developed acute false aneurysms during the early postoperative period and underwent urgent reoperations to correct this serious complication. One patient was found to have an unexplained rent in the center of the patch and awakened after its replacement with a contralateral monoparesis that resolved within the following week. The remaining two patients had anastomotic disruptions. One was repaired successfully but the other recurred because of infection 1 month later and required carotid ligation. Neither of these patients sustained neurologic deficits.

Clinical Correlations. The risk of early stroke or thrombosis is correlated with selected clinical features in Table 4. The results of patch angioplasty were measurably superior only with respect to the stroke rate among patients with patent contralateral internal carotid arteries (0.3% VP, 3.2% NP; $p = 0.0085$) and the incidence of postendarterectomy occlusion among men (0.4% VP, 4.1% NP; $p = 0.005$). Nevertheless, these data also suggested several other trends even though they could not be fully confirmed by statistical testing. Patch closure was associated with three to five times fewer perioperative strokes in women and in patients with previous neurologic symptoms. Moreover, patching appeared to discourage carotid thrombosis irrespective of whether antiplatelet agents had been administered before surgery ($0.05 < p < 0.1$). Considering all complications (death, stroke, thrombosis, patch disruption) and counting no patient twice, the combined surgical morbidity and mortality rate was 2.4% (9/368) when patches were applied and 6.0% (26/433) when they were not ($p = 0.015$).

Late Results

Survival. Cumulative survival and the number of eligible patients at each follow-up interval are illustrated in Figure 2. A total of 294 entrants were available for consideration during the third postoperative year, and the survival rates for the VP and NP cohorts at the conclusion of the study period were 80 and 87%, respectively. Attrition was comparable among symptomatic and asymptomatic surgical candidates, and none of the actuarial differences was statistically significant. Of 81 late deaths, 28 (35%) were attributed to cardiac disease, 11 (14%) to cancer, and nine (11%) to cerebrovascular events. Fatal strokes have occurred in only 1.1% of each treatment group (4 VP, 5 NP).

Neurologic events. There were 31 perioperative TIAs, strokes or deaths. Of the remaining 770 patients, 42 (5.4%) have experienced subsequent neurologic symptoms involving the ipsilateral (N = 27, 3.5%) or contralateral cerebral hemisphere (N = 15, 1.9%) during a mean follow-up interval of 20 months. Completed strokes have occurred on the same side as previous carotid endarterectomy in 11 (2.7%) of the 412 patients in the NP group and in seven (2.0%) of the 358 who received patch angioplasty. Figure 3 illustrates the cumulative incidence of all ipsilateral neurologic events in the entire series. None of the observed differences was statistically valid beyond the early postoperative period. Therefore, patching did not appear to influence the late stroke rate.

Recurrent stenosis. There were 21 perioperative deaths or internal carotid occlusions. Only ten (1.1%) of the remaining 896 endarterectomies (3 VP, 0.7%; 7 NP, 1.5%) have required reoperations for recurrent stenosis during the follow-up period (Fig. 4). As indicated in Table 5, however, objective reassessment has been obtained for just 332 arteries (37%) despite the fact that all patients were encouraged to schedule annual DSA or Doppler ultrasound examinations for at least 3 years after their original procedures. Recurrent lesions (≥30% of lumen diameter) have been documented with this approach in 4.8% of the VP group and in 14% of the NP group ($p = 0.0137$). Furthermore, the cumulative recurrence rate (Fig. 5) was 9% and 31%, respectively ($p = 0.0066$). The actuarial difference between the VP and NP cohorts (3.7% VP, 39% NP) was especially significant ($p = 0.0019$) when asymptomatic carotid stenosis had been the initial indication for surgical treatment.

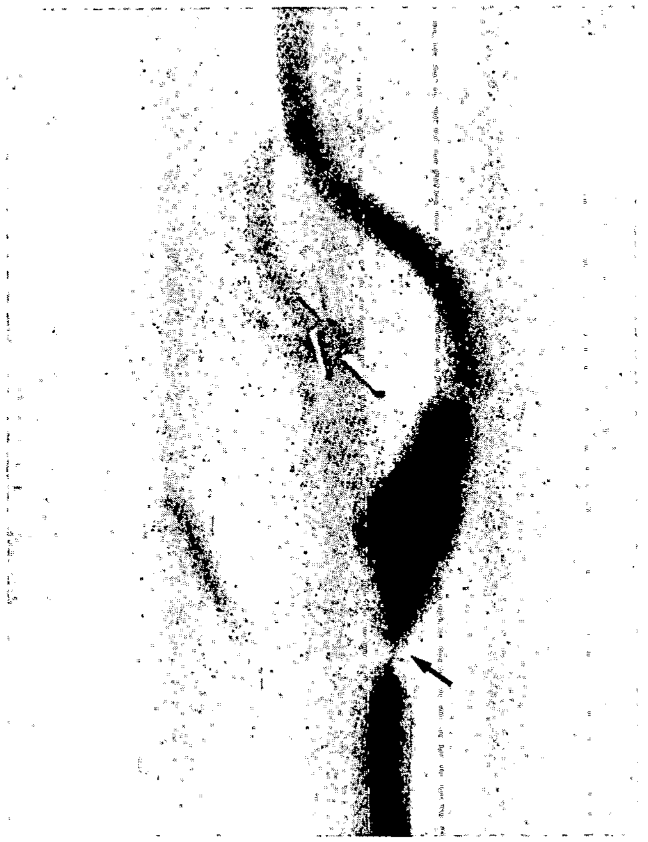

FIG. 4. Intra-arterial digital subtraction angiogram demonstrating a high-grade "collar" senosis (arrow) at the junction of the common carotid artery and the saphenous vein patch 1 year after carotid endarterectomy.

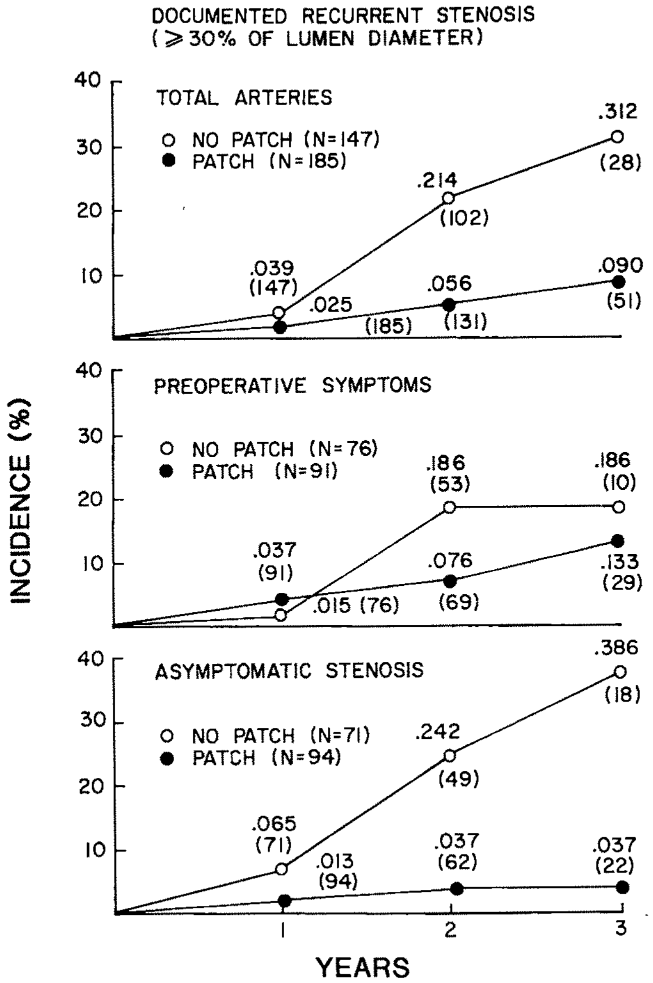

FIG. 5. The cumulative incidence of recurrent lesions (≥30% stenosis) in 332 arteries documented by objective carotid imaging. The number of vessels under consideration at each interval is enclosed in parentheses.

Discussion

Despite lingering controversy concerning its perceived overuse, countless studies have established that carotid endarterectomy is an exceedingly effective approach to stroke prevention in selected patients, provided its immediate risk meets acceptable standards. Previous reports from the Cleveland Clinic indicated that surgical treatment should be a serious consideration for either symptomatic or asymptomatic patients who have severe (≥70%) carotid stenosis or advanced, bilateral bifurcation disease.[18-20] Moore et al.[21,22] have presented similar data, but the fact remains that long-term benefit in appropriate candidates is greatly compromised by excessive complication rates at the centers in which their procedures are to be performed. Since acute or unstable strokes and chronic hemiplegic deficits now are universally accepted as contraindications to surgical intervention, poor results after extracranial reconstruction generally reflect imperfect surgical technique. There is abundant evidence that carotid endarterectomy *can* be done safely, and if surgeons are to respond effectively to their critics, it *must* be done safely.

In addition to reservations about its early risk, there currently is speculation concerning the durability of carotid endarterectomy. Although large, retrospective in-

TABLE 5. *Recurrent Stenosis During a 3-Year Interval Following 896 Carotid Endarterectomies**

Recurrent Carotid Stenosis	No Patch (N = 466)		Patch (N= 430)	
	No.	%	No.	%
Reoperations	7	1.5	3	0.7
Objective follow-up imaging	146	31	186	43
Documented lesions	21	14	9	4.8
30–49%	5	3.4	4	2.2
50–69%	6	4.1	1	0.5
70–89%	6	4.1	1	0.5
≥90%	2	1.4	1	0.5
Occlusion	2	1.4	2	1.1

* Operative deaths and early occlusions have been omitted.

vestigations have suggested that the incidence of recurrent stenosis warranting reoperation is 3% or less, this conclusion necessarily was based on incomplete follow-up and imprecise criteria (new symptoms or cervical bruits) for diagnostic angiography.[23-27] Since the introduction of noninvasive hemodynamic testing and carotid imaging, however, recurrence rates have been reported to be substantially higher than expected in small series of patients who were evaluated prospectively. According to several of these studies, recurrent stenosis exceeding 50% of lumen diameter occurred in 9–19% of patients within 2–5 years after conventional endarterectomy.[28-32] The vast majority of these lesions were caused by myointimal hyperplasia, and this complication appeared to be especially common in women and in cigarette smokers.[33,34] Even if the perioperative risks of carotid endarterectomy were negligible, an unacceptable incidence of early hyperplastic recurrence undoubtedly would be cited as sufficient reason not to correct primary asymptomatic stenosis irrespective of its severity.

Sundt,[35] Imparato,[36] and their associates have long maintained that patch angioplasty was singularly important in the reduction of early morbidity and late recurrence throughout their extensive experience with carotid reconstruction. Archie[37] also found that vein patching eliminated neurologic complications and recurrent hyperplastic stenosis in his series of 200 prospectively randomized operations, and Deriu et al.[38] described similar success with prosthetic patch material following 86 procedures. In our study of over 900 endarterectomies, saphenous patch angioplasty was associated with perioperative strokes in 0.7% and internal carotid thrombosis in 0.5%. In comparison, early strokes ($p = 0.0084$) or occlusions ($p = 0.0027$) each occurred after 3.1% of routine arteriotomy closures. Although their clinical importance is not yet known, recurrent defects were objectively documented in only 4.8% of the patch group during the first 3 postoperative years, compared with 14% of the NP group ($p = 0.0137$).

This investigation has at least two unique features. First, it contains a sufficient number of patients and operations that its conclusions should be reliable. Second, neither treatment cohort was prejudiced by poor results. If VP angioplasty can make good results even better at our center, then it could substantially enhance the mediocre outcome that apparently is encountered at many others. The success of the saphenous patch probably is related to several factors. Clearly, it alters the configuration of the carotid bulb by making it larger.[36] In addition, its intimal surface may prevent early microembolic strokes and carotid thrombosis by discouraging platelet aggregation at the endarterectomy site. Finally, it may reduce the incidence of myointimal hyperplasia by promoting rapid endothelial coverage of the bifurcation.

The adjunctive use of a shunt is a logical consideration simply because patch angioplasty takes more time than primary closure. Accordingly, surgeons who ordinarily prefer not to shunt might choose to restrict patching to specific subsets of patients who seem to have the most to gain from this precaution. Women comprise one such group because of the small size of their carotid arteries and their propensity for hyperplastic recurrence, and patients with contralateral internal carotid occlusions are another because their risk for perioperative stroke is relatively high under any circumstances.[39,40] Whatever the criteria for its use, our experience suggests that patch angioplasty helps to fulfill the high expectations that surgeons, patients, and critics alike have established for carotid endarterectomy: the early results must be perfect, and the late results have to stay that way.

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Effect of Optimization of Hemodynamics on Fibrinolytic Activity and Antithrombotic Efficacy of External Pneumatic Calf Compression

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External pneumatic calf compression is effective but imperfect for antithrombotic prophylaxis in surgical patients. In preliminary studies, sequential filling of multisegmented leggings with graded pressure decreasing from ankle to knee increased venous flow velocity and wall shear stress, decreased residual venous volume, and enhanced postoperative fibrinolysis more than uniform compression. To determine if improved hemodynamics also increased antithrombotic activity, we performed a prospective randomized trial in neurosurgical patients comparing sequential application of graded pressure with uniform pressure applied to either a segmented bladder or to a single bladder. Deep vein thrombosis was diagnosed by leg scanning and impedance plethysmography and confirmed by phlebography. Venous thrombosis developed in 3 of 45 patients with graded-sequential filling, 6 of 50 with uniform compression-multiple compartments, and 3 of 41 with uniform pressure single bladder (differences not significant). These results suggest either that uniform compression offers all that can be expected of external pneumatic calf compression in prevention of venous thrombosis, or that even if a study with greater statistical power showed graded-sequential filling to be superior, the benefit/cost ratio of the more complex latter system is not likely to be large.

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ALTHOUGH THE INCIDENCE of deep vein thrombosis in postoperative patients can be reduced by prophylactic administration of antithrombotic drugs, such preventive measures have not been universally adopted into practice. Several surveys[1-3] have reported that many practitioners use prophylactic antithrombotic drugs only in their highest risk patients, if they use them at all. The efficacy of prophylactic administration of anticoagulants and antiplatelet agents is disputed, and is certainly not absolute; failures do occur. The requirement for laboratory control, at least with warfarin, is also a deterrent. The most prominent obstacle to wider adoption of antithrombotic prophylaxis, however, has been the fear of bleeding complications, which inevitably to some degree attend the use of antithrombotic drugs in surgical patients.

An alternative approach, attractive because of its freedom from hemorrhagic side effects, is the use of physical methods to reduce pooling of venous blood in the lower extremities and to increase the velocity of venous blood flow. Such physical techniques include elastic stockings, passive leg exercises, electrical calf stimulation, and external pneumatic compression of the legs. The latter has been most extensively studied and appears to be most effective among the physical methods available.

A substantial literature has developed regarding the use of external pneumatic compression boots or leggings in patients at risk of venous thromboembolism, including patients undergoing neurologic operations,[4-6] urologic surgery,[7,8] general surgical procedures for malignant or benign disease,[9,10] operations for gynecologic malignancy,[11] orthopedic procedures,[12,13] and nonoperative conditions.[14] The mechanism of action of external pneumatic compression in reducing the rate of venous thrombosis in the lower limbs is conjectured to be twofold: a fluid mechanical effect expelling blood from the lower extremities to substitute for the action of the inoperative muscle pump in the recumbent patient, and enhancement of fibrinolytic activity.[15] The relative in-

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fluence of these two factors is not certain. External pneumatic compression appears to be associated with no bleeding complications even in patients undergoing extensive surgery.

Although external pneumatic compression of the legs has proven efficacious in reducing the rate of venous thrombosis, there are occasional failures associated with its use, particularly in high risk patients. In our trial of calf compression in neurosurgical patients,[4] for example, 9% of patients who were treated with external pneumatic compression developed deep vein thrombosis (compared with 25% in the control group). As conventionally applied, external pneumatic calf compression may not produce an optimal hemodynamic effect. It is possible that an improvement in the fluid mechanical aspects of the procedure, brought about by modifications in the apparatus, would be reflected in an increase in its antithrombotic effectiveness.

Shapiro and associates have conducted an extensive study of the hydrodynamics of external pneumatic compression, first in theoretical and experimental circulation models[16] and later in human volunteers using gated blood pool scans of the lower extremities.[17] They compared the amount and rate of blood expelled when different modes of intermittent external pneumatic compression were applied to the lower extremities. Scintillation camera imaging of the labelled red cell pool synchronized to the pressurization cycle provided data on the time course of changes in regional blood volumes in the leg. They calculated regional values of the fraction of blood ejected as well as comparative indices proportional to flow rate, blood velocity, and wall shear stress, all of which might reasonably be regarded as figures of merit to be maximized in an attempt to obtain optimal prophylaxis against deep vein thrombosis. Using a four-compartment cuff, they studied compression modes with different intercompartmental pressure gradations and different intercompartmental intervals to the onset of pressurization. The most effective system hemodynamically was found to be a four-compartment legging in which the bladders filled in sequence beginning at the ankle with graded pressures decreasing from ankle to knee. The optimal values for a four-compartment system were approximately 60, 50, 40, and 30 mmHg, decreasing from ankle to knee, with about 0.25 sec between pressurizations of successive segments, a pressure rise time of less than 0.5 sec, each segment held at full pressure for about 10 sec, and a period of about 50 sec with pressure relieved before the next cycle. No commercially available system is hemodynamically optimal or conforms to these features.

We tested the hypothesis that an external pneumatic compression device with these characteristics would improve antithrombotic efficacy in patients undergoing neurosurgical operations, a high-risk group that cannot safely be given antithrombotic drugs because of the hazard of intracranial bleeding complications. A corollary of this hypothesis would be that graded-sequential filling of such a specially designed apparatus would have sufficiently improved antithrombotic properties to justify its increased cost and complexity. We also studied the effect of different modes of calf compression on whole blood fibrinolytic activity to explore further the mechanism of the antithrombotic action of external pneumatic compression.

Methods

The trial was initiated as a two-armed clinical study with randomization afforded by a series of sealed envelopes. Patients were assigned either to receive uniform compression delivered by a four-compartment system applied to the calf (Group II), with all compartments filled simultaneously to the same pressure, or to have sequential filling of the same system from ankle to knee with graduated pressure decreasing from ankle to knee (Group I) according to specifications derived from the studies of Kamm et al.[17] with pressure and timing values as stated above. The apparatus was furnished by Gaymar Industries, Inc., Orchard Park, NY. The four-segment cuffs had "wavy" boundaries between segments, a configuration that effectively eliminated the pooling of blood that, in the scintillation studies of Kamm et al., had been observed to occur between segments of more conventional four-segment cuffs.

The study was conducted in patients undergoing neurosurgical operations at the Beth Israel Hospital. A description of the patient population is presented in Table 1. External pneumatic compression was applied during the induction of anesthesia, except for two patients (1 in Group I and 1 in Group II) in whom confinement to bed before operation suggested the need for earlier prophylaxis. In these cases the external pneumatic compression device was applied as soon as the patient came to the attention of the investigators.

Diagnosis of deep vein thrombosis was made by ^{125}I-fibrinogen scanning,[18] which was begun on the first postoperative day, impedence plethysmography (IPG)[19] every second day, and ascending phlebography by the technique of Rabinov and Paulin[20] in patients who had positive fibrinogen scans or IPGs. In addition, blood was drawn before operation and at intervals in the postoperative period for determination of fibrinolytic activity in heparinized whole blood by a radioactive clot lysis technique modified by Coppe et al.[21] from the method of Moroz.[22] General surgical patients undergoing operations for nonthrombotic conditions were also studied as controls for the fibrinolysis assay. Patients were main-

TABLE 1. *Patient Groups*

	Group I Graded-Sequential	Group II Uniform Pressure, Four Compartment	Group III Single Bladder
No. of patients	45	50	41
Sex (M/F)	24/21	23/27	20/21
Age 10–20	0	0	0
21–30	9	4	6
31–40	10	8	4
41–50	8	16	8
51–60	8	8	8
61–70	6	5	8
71–80	2	8	7
>80	2	1	0
Surgical procedure			
Craniotomy for tumor	4	6	5
Shunts	6	5	5
Other craniotomies	9	9	5
Cervical laminectomy	7	9	8
Lumbar laminectomy	13	14	12
Spinal fusion	6	7	6
Risk factors for DVT			
Previous DVT or PE	4	1	2
Obesity	10	8	10
Varicose veins	3	2	2
EACA	1	0	0

tained on external pneumatic compression until they became ambulatory or for a maximum of the period spanned by three injections of labelled fibrinogen, roughly 3 weeks.

After 43 patients had been entered into the trial, Group III, receiving uniform compression with a single bladder system (Venodyne, Lyne-Nicholson, Inc.), was added to provide a realistic comparison of graded-sequential filling *versus* a commercially available system having uniform pressurization. The randomization was adjusted to balance the three patient groups. It should be noted that the Venodyne system has a substantially longer pressure rise time than do the other systems studied.

For ethical reasons no unprotected control group was included in this study, which instead compared a technique of established effectiveness *versus* another form of treatment that was potentially superior. This protocol was approved by the Institutional Review Board at the Beth Israel Hospital.

Results

One hundred fifty-eight subjects were enrolled in the study, but 22 were dropped prior to its completion because of nonadherence to the study protocol in 13 patients, including two who refused the procedure because of discomfort, nonoperative therapy (5 patients), or failure of the apparatus (4 patients). Forty-five of the remaining 137 patients were in Group I, 50 in Group II, and 41 in Group III. The surgical procedures, age, sex, and other relevant clinical details are shown in Table 1. The groups appeared to be comparable in all important respects, except that patients in Group I had a somewhat higher prevalence of risk factors for venous thrombosis.

Compression of the limbs is known to enhance systemic fibrinolytic activity, which might augment the antithrombotic action of external pneumatic compression. We studied whole blood fibrinolytic activity in the first 75 patients. A fall in fibrinolytic activity is characteristic of postoperative patients, beginning in the first 24 hours after operation and reaching its nadir by the third postoperative day.[23,24] Such a reduction in fibrinolytic activity was exhibited by the group of general surgical patients studied as controls (Fig. 1; $p < 0.01$ preop *vs.* postop day 1, Friedman's rank sum test). Patients who received external pneumatic compression of the limbs with a uniform compression device, either in Group II or Group III, failed to display this expected fall in fibrinolytic activity in the postoperative period and, in fact, 9 of 16 patients (56%) with the single bladder system and 21 of 35 (60%) with the four-compartment uniform compression system showed an *increase* in the fibrinolytic index on the first postoperative day (Figs. 1 and 2).

Patients in Group I had an average increase in fibrinolytic activity that was significantly greater in magnitude than for those in Groups II and III (mean fibrinolytic index on first postop day 1.45 for graded sequential group *vs.* 1.06 for single bladder system and 1.12 for multiple bladder system with uniform compression; $p < 0.02$ by Dunnett's test or Kruskal-Wallis test), and 23 of 25 patients (92%) with graded sequential filling had a rise in activity. Thus the effect on fibrinolytic activity was correlated with the hemodynamic effectiveness of the external pneumatic compression systems. Patients who failed to be protected by external pneumatic compression, and who developed venous thrombosis despite its use, typically also failed to develop enhanced fibrinolytic activity as a result of the application of external pneumatic compression after operation. Six of the eight such patients whose fibrinolytic index was assessed on the first postop day had values below their group mean (Fig. 2). Patients whose level of fibrinolytic activity was increased did not exhibit any clinically obvious bleeding tendency as a result, but blood loss was not measured and this issue was not rigorously appraised.

The effect of the treatments on the incidence of deep venous thrombosis is shown in Table 2. All patients who developed a positive fibrinogen scan or IPG were requested to have a phlebogram to confirm the diagnosis of venous thrombosis, but five refused. Fifteen patients developed a positive fibrinogen scan; ten of these had a phlebogram, three of which proved to be negative. These three patients are regarded as "false positives," although the positive scan may have been related to venous thrombosis in a muscular tributary of the deep venous system that was not visible on phlebography. For purposes of analysis, "positive" patients are considered to be those who have a positive scan with a positive (confirmatory) phlebogram plus those who had a positive scan but did not have a phlebogram.[4] The results of such an analysis suggest a trend toward a greater antithrombotic effect for graded sequential filling than for the uniform pressure four-compartment system, but no difference from the single bladder uniform compression system. The differences are not statistically significant. The 95% confidence interval for the difference between graded sequential compression and uniform compression with multiple segments is from −16.9% to 6.3%, and for the difference between graded sequential compression and uniform compression with a single bladder it is from −11.4% to 10.2%. The fact that these intervals include zero is consistent with the lack of statistical significance.[25]

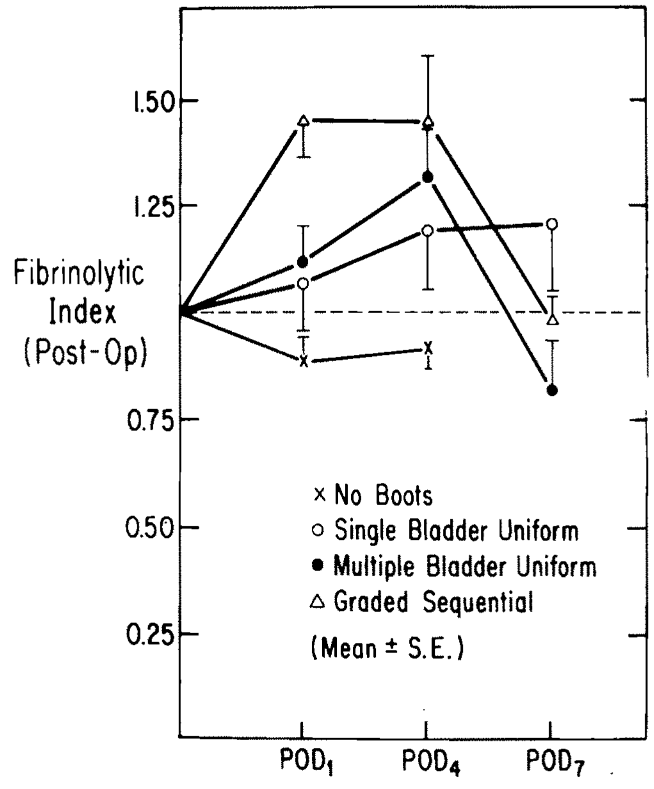

FIG. 1. Fibrinolytic activity in the three patient groups on the first, fourth, and seventh postoperative days. Analogous values are also shown for general surgical patients undergoing operations of comparable severity ("no boots"). Results are expressed as a "fibrinolytic index" (cpm released into supernatant divided by cpm originally contained in radioactive clot) and are normalized to preoperative values for each patient.

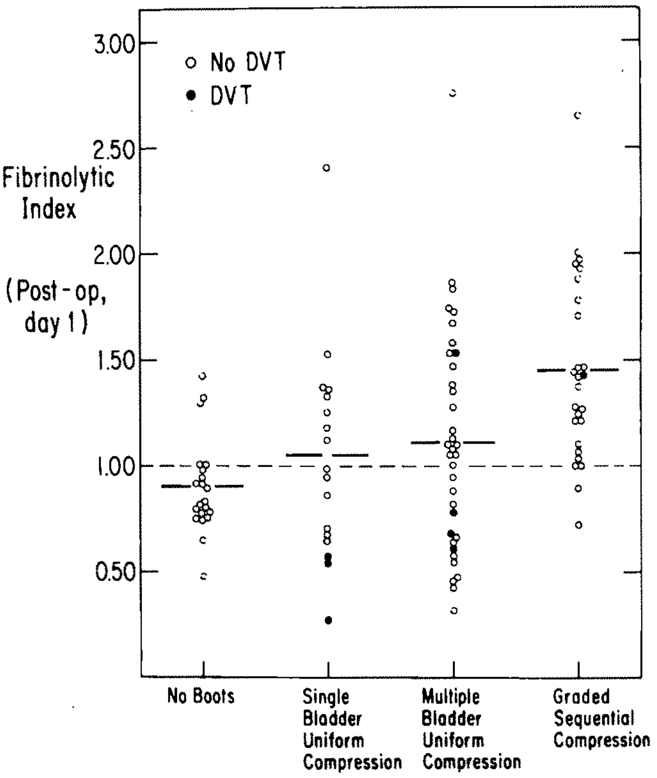

FIG. 2. Fibrinolytic index on the first postoperative day in the four patient groups. Horizontal bars indicate mean values. Closed circles indicate patients who subsequently developed deep vein thrombosis.

The same conclusion will be reached if one considers as "positive" only those patients who had a positive scan with a positive (confirmatory) phlebogram or if one includes as positive all patients with a positive scan regardless of the phlebogram.

We calculated that if the present rate of venous thrombotic complications were maintained, approximately 500 patients in each group would be required to show a statistically significant difference between Group I and the other groups with an alpha error <0.05 and a beta error of 0.20.[26] Because this was considered impractical the study was terminated at this time.

Discussion

External pneumatic compression is an established form of prophylaxis for prevention of venous thrombosis in postoperative patients. The relative importance of enhanced fibrinolysis and of physical dispersion of the components of a thrombus by hemodynamic factors in calf compression is not known. In this study they tended to vary together. The failure of fibrinolytic activity to be enhanced by pneumatic compression in patients who subsequently developed venous thrombosis was predictable. The association of long whole blood clot lysis times with subsequent venous thrombosis in surgical patients

TABLE 2. *Deep Vein Thrombosis*

	Group I Graded Sequential Compression	Group II Uniform Pressure, Multiple Compartment	Group III Uniform Pressure, Single Bladder
N	45	50	41
A. + scan + venogram	2	3	2
B. + scan no venogram	1	3	1
C. + scan − venogram	0	2	1
DVT: A + B	3/45 (6.7%)	6/50 (12%)	3/41 (7.3%)
A + B + C	3/45 (6.7%)	8/50 (16%)	4/41 (9.8%)
A only	2/45 (4.4%)	3/50 (6%)	2/41 (4.9%)
Development of DVT, postop days	2, 4, 7	1, 2, 5, 5, 12, 13	2, 2, 3
DVT, (A + B), operation	Craniotomy for tumor Laminectomy (2)	Craniotomy for tumor (2) Craniotomy for trauma Other craniotomy (2) Laminectomy	Craniotomy for tumor Laminectomy, Harrington rod

was observed by Comp and associates,[27] and Clayton et al.[28] found low levels of fibrinolytic activity to be a sensitive predictor of venous thrombosis in patients undergoing gynecologic operations.

The evidence for the efficacy of pneumatic compression is persuasive, but calf compression might be even more effective if its hemodynamic effects were optimized. Among the four fluid mechanical parameters influenced by external pneumatic compression (flow velocity, volume flow rate, shear stress, and residual volume of blood in the limbs), it is not yet possible to decide which is most important for antithrombotic effectiveness of the system; however, since under normal circumstances they all tend to vary together, this point may be moot. It is clear that commercially available systems for applying external pneumatic compression to the lower limbs are not optimized in these respects.

We found that a system for external pneumatic compression in which the pressure was applied in a graded fashion, milking the blood from ankle to knee, was more effective hemodynamically, and in the clinical trial it proved to be more effective in enhancement of fibrinolytic activity than uniform compression applied to the leg either in a multiple bladder system or in a single bladder. Nicolaides et al.[29] have previously reported that a multiple bladder system involving sequential filling from ankle to thigh but with uniform pressure was more effective in accelerating femoral venous flow and was superior to a single bladder system in preventing proximal venous thrombosis in patients undergoing abdominal operations; however, there was no significant difference in the rate of calf thrombi. Since the sequentially filled device in their trial had thigh cuffs as well as calf cuffs and the single bladder system had only calf compression, it is not certain that the difference in the frequency of proximal (thigh) thrombi was attributable to the sequential filling. In a subsequent study, Nicolaides et al.[30] compared the sequentially filled device applied for at least 3 days and followed by elastic stockings *versus* electrical calf stimulation *versus* low-dose heparin, and they found the results of external pneumatic compression and heparin to be roughly equivalent. In the system employed by Nicolaides et al., the filling pressures, rise time, duration of filling, and interval beteen successively filled bladders were different from the corresponding values employed in the optimized device we have studied, which is not duplicated by any commercial unit now available.

Despite the improved hemodynamic effectiveness of the graded compression sequentially filled system and the superior biologic effects reflected by enhanced fibrinolytic activity, we were unable to show greater antithrombotic effectiveness for this device. There were no significant differences in the frequency of venous thrombosis in the three patient groups. Two possible explanations are: (1) regardless of the difference in hemodynamic effects, the difference in antithrombotic effectiveness among the three modes of external pneumatic compression is negligible, and the uniform compression system accomplishes all that can be expected of external pneumatic compression in respect to prevention of venous thrombosis, or (2) a real difference exists, with graded sequential compression being superior to uniform compression, but because of the limited number of patients or for other reasons, the study was insufficient in statistical power to show the difference (*i.e.*, there is a possibility of a beta error).[31] Even if the latter is true, however, the difference in efficacy of the three forms of calf compression is probably not large, and one must question whether the increment in clinical benefit would be worth the additional cost and complexity of engineering and producing the graded sequential filling system.

It remains possible that, in a population at even higher risk than the neurosurgical patients (such as those with reconstructive operations on the hip), a hemodynamically superior system applying graded pressure with sequential filling might have demonstrably better antithrombotic efficacy than systems in which fluid mechanical features are not optimized.

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Pulmonary Hypertension and Leukosequestration after Lower Torso Ischemia

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Ischemia stimulates thromboxane (Tx) synthesis. This study tests the hypothesis that the cardiopulmonary dysfunction that may follow aortic declamping is related to Tx. Anesthetized dogs ($N = 15$) were subjected to 4 hours of infrarenal aortic cross-clamping. In untreated control animals ($N = 7$), plasma levels of TxB_2 rose from 654 ± 74 pg/mL to 1238 ± 585 pg/mL at 5 min ($p < 0.05$), and to 3174 ± 912 pg/mL 3 hours after declamping ($p < 0.05$). Mean pulmonary artery pressure (MPAP) rose 5 min after declamping from 13 ± 2 mmHg to 21 ± 2 mmHg ($p < 0.05$). Cardiac Index (CI) declined during ischemia from 181 ± 30 mL/kg · min to 128 ± 16 mL/min · kg ($p < 0.05$), and to 80 ± 8 mL/min · kg after 4 hours of reperfusion ($p < 0.05$). Platelet counts declined but platelets labeled with In-111 did not accumulate in the lungs, whereas quantitative counts of polymorphonuclear leukocytes (PMN) in the lungs 4 hours after declamping yielded 213 ± 33 PMN/25 high power fields (HPF) in dependent areas of the lung and 153 ± 26 PMN/25 HPF in nondependent areas. The wet/dry weight ratio of the lungs was not elevated, although foci of proteinaceous exudate and PMNs in alveoli were noted. Another group of dogs ($N = 8$) were pretreated by random choice with the Tx synthase inhibitor OKY-046 2 mg/kg IV every 2 hours, which led to: lower TxB_2 levels at baseline 95 ± 35 pg/mL ($p < 0.05$), 5 min after ischemia 140 ± 93 pg/mL and after 3 hours of reperfusion 122 ± 36 ($p < 0.05$); lower MPAP, 16 ± 2 mmHg ($p < 0.05$); higher CI throughout ($p < 0.05$); normal histology and reduced pulmonary PMN sequestration both in dependent 127 ± 15 PMN/25 HPF and nondependent areas of the lungs 95 ± 11 PMN/25 HPF ($p < 0.05$). In animals undergoing sham ischemia ($N = 3$), levels of TxB_2 and cardiopulmonary function remained unchanged from baseline. There were 150 PMN/25 HPF in dependent and 85 PMN/25 HPF in nondependent lung areas. The results indicate that ischemia-generated Tx mediates a rise in MPAP, a fall in CI, and PMN entrapment in the lungs.

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THE CARDIOPULMONARY DYSFUNCTION that occasionally accompanies abdominal aortic aneurysm surgery is thought to be due to microaggregates released from the ischemic lower torso.[1-3] Experimental work has documented intrapulmonary clot formation as well as platelet and neutrophil accumulations in the lungs following release of an occluding aortic clamp. The associated decline in cardiac output and increase in pulmonary microvascular permeability has been theorized to be related to activation of circulating blood cells (*i.e.*, platelets and polymorphonuclear leukocytes). Products of these cells, such as proteases and oxygen-free radicals, are thought to be the direct mechanism of injury.

Ischemia of a limb is a stimulus to the synthesis of TxA_2.[4] A rise in plasma and hind limb lymph Tx levels were noted during the period of postischemic reperfusion.[5] This vasoactive proaggregatory prostenoid may be partially responsible for the activation and accumulation in the lungs of circulating blood cells. This study was designed to test the thesis that blood cell accumulations in the lungs following lower torso ischemia are related to TxA_2.

Methods

Eighteen female greyhound dogs weighing 22–30 kg were anesthetized with pentobarbital sodium, 15–20 mg/kg IV and paralyzed with 2 mg pancuronium bromide. The dogs were intubated and ventilated with room air at a tidal volume of 15 mL/kg and rate of 12 to

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15 cycles/minute to achieve an arterial PCO_2 of 30–35 mmHg. The state of anesthesia and paralysis were maintained by a continuous infusion of pentobarbital (0.1 mg/kg • min) and pancuronium (30 μg/kg • min). The animals were placed supine and catheters passed into the aorta *via* the right carotid artery and into the right atrium *via* the right jugular vein. A 7 French thermistor-tipped pulmonary arterial catheter (Electro-Catheter Corp., Rahway, NJ) was introduced through the left jugular vein, and a Foley catheter placed into the urinary bladder.

In 15 dogs the infrarenal aorta was mobilized through a midline laparotomy. All distal branches were ligated and transected, including the internal iliac and the median caudal arteries. The aorta was occluded with a pediatric vascular clamp just below the renal arteries and the abdomen loosely closed. After 4 hours the abdomen was reopened and the aortic clamp removed. Three animals underwent laparotomy without aortic clamping and served as a sham group. Lactated Ringer's solution was administered to maintain a pulmonary arterial wedge pressure of 4 mmHg. External heat was used to stabilize body temperature between 36 to 37 C. Strain gauge transducers (Model D-240, Benley Laboratories, Inc., Irvine, CA) were used to measure the following pressures: mean arterial (MAP), mean pulmonary arterial (MPAP), and pulmonary arterial wedge (PAWP). Cardiac output, determined by thermodilution (Model 801, Instrumentation Laboratory, Lexington, MA) was performed in triplicate and divided by body weight to obtain cardiac index (CI).

Blood gases, pH, oxygen saturation, and hemoglobin of arterial and mixed venous blood were measured with Clark and Severinghaus electrodes and by spectrophotometry using extinction coefficients specific for dog blood (Instrumentation Laboratory, Model 813 and 282). Physiologic shunting ($\dot{Q}S/\dot{Q}T$), the per cent of blood exiting the lungs with the same oxygen content as mixed venous blood, was calculated from the Berggren equation:[6]

$$\frac{\dot{Q}S}{\dot{Q}T} = \frac{CcO_2 - CaO_2}{CcO_2 - C\bar{v}O_2} \times 100$$

where $\dot{Q}S$ is shunt flow, $\dot{Q}T$ is total flow, CaO_2 and $C\bar{v}O_2$ are oxygen contents in arterial (a) and pulmonary arterial ($\bar{v}$) blood. CcO_2 is the oxygen content in capillary blood derived from the alveolar gas equation assuming a respiratory quotient of one. Platelets and leukocytes were counted by means of phase microscopy. Plasma concentrations of thromboxane (Tx) B_2 and 6-keto-$PGF_{1\alpha}$, the stable hydrolysis products of TxA_2 and prostacyclin, respectively, were measured by use of a double antibody radioimmunoassay.[7–9] Blood was drawn into tubes containing ethylene diamine tetracetic acid (EDTA) anticoagulant and aspirin. The blood was centrifuged at 1500 × g for 20 minutes and the plasma separated and stored at −20 C until assayed.

To assess pulmonary entrapment of circulating blood cells, surface counting of In-111-labeled autologous platelets was done in three animals while quantitative histology was done to assess leukocyte sequestration. White blood cell separation and labeling was not done because of our past experience, which indicated that the method itself would activate these cells and lead to their pulmonary entrapment. Just after anesthesia, 200 mL blood was drawn in acid-citrate dextrose solution and replaced with 300 mL of Ringer's Lactate. Platelet concentrates were isolated from the blood in a 22 C refrigerated centrifuge (International Equipment Co, Needham Heights, MA). The blood was spun at 3200 × g for 4 minutes. Platelet-rich plasma (PRP) was removed and the concentrated red blood cells were returned to the animal. The PRP was centrifuged at 5500 × g for 5 minutes and the supernatant decanted. The PRP was washed with 100 mL of 0.9% sodium chloride, spun, and after the supernatant was decanted, 50 mL of 0.9% sodium chloride was used to resuspend the platelets. One mCi of In-111-oxine (New England Nuclear, Boston, MA) was added and, after a 30-minute incubation in a 37 C water bath, the platelets were washed and resuspended in 50 mL of platelet-poor plasma prior to transfusion.

In order to minimize entrapment in the surgical wound, the labeled platelets were infused following the operative procedure, which was 10 minutes prior to aortic clamping. One-inch collimated sodium iodide crystals were mounted over both lung fields as well as the upper and lower extremities. Location of the external detectors was maintained constant throughout the experiment. Counts were collected 10 minutes after platelet infusion, just prior to arotic clamping, and thereafter at 30-minute intervals.

Animals were pretreated with saline placebo (N = 7) or the Tx synthase inhibitor OKY-046 2 mg/kg (N = 8) IV, every 2 hours, starting 30 minutes prior to surgery. Sham animals (N = 3) were treated with saline. Monitoring was continued for 8 hours, that is 4 hours of aortic clamping and 4 hours of reperfusion. The dogs were then killed with an overdose of IV potassium. The lower lobe of one lung was removed and the wet to dry ratio of the bloodless lung determined. Gluteraldehyde introduced *via* the endotracheal tube was then used to inflate the lungs for 20 minutes at a constant pressure equivalent to a 25-cm column of water. The trachea was then ligated and the lungs removed and bathed in gluteraldehyde for 24 hours. Specimens of lung were taken from dependent (posterior) and nondependent (anterior) regions. After hematoxilin and eosin staining, polymor-

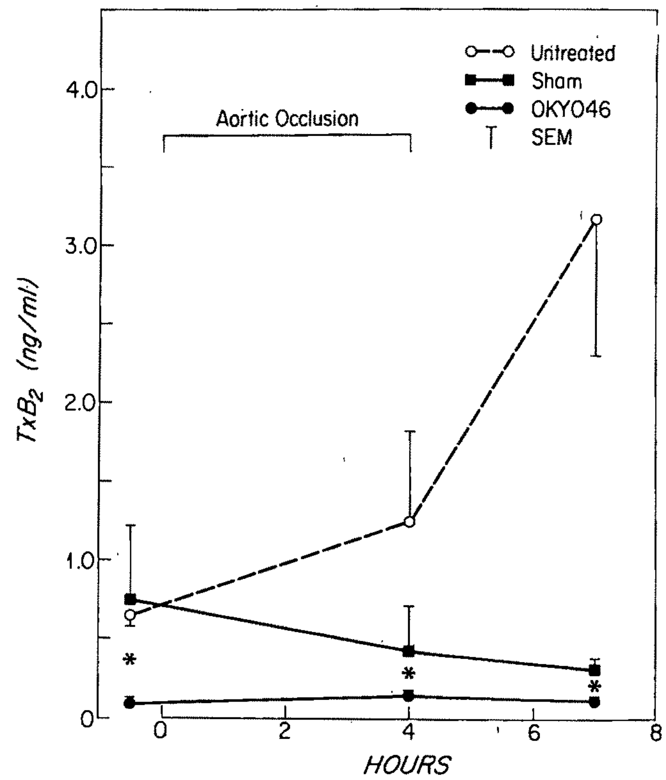


FIG. 1. Four hours of infrarenal aortic occlusion led to a rise in plasma TxB_2 5 minutes after clamp release. Synthesis of Tx was most prominent later during reperfusion. Pretreatment with OKY-046 prevented TxB_2 synthesis. Asterisks refer to significant differences between OKY-046 and placebo-treated groups.

phonuclear leukocytes (PMN) were counted in 25 high powered fields (HPF) from each region. All data are presented in text and figures as mean ± standard error. Statistics are based on a two-way analysis of variance, paired and nonpaired t-test. Significance was accepted if $p < 0.05$.

Animals used in this study were maintained in accordance with the guidelines of the Committee on Animals of the Harvard Medical School and those prepared by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Animals Resources, National Research Council (DHEW publication No. (NIH) 78-23, revised 1978).

Results

Aortic cross-clamping in placebo-treated animals resulted in a rise of TxB2 levels in mixed venous blood from a baseline level of 654 ± 74 pg/mL to 1238 ± 585 pg/mL ($p < 0.05$) at 5 minutes and 3174 ± 912 pg/mL after 3 hours of reperfusion ($p < 0.05$) (Fig. 1). Mean pulmonary arterial pressure rose from a value of 13 ± 2 mmHg prior to ischemia to 21 ± 2 mmHg, 5 minutes after reperfusion ($p < 0.05$). Ninty minutes after reperfusion, MPAP levels had returned to baseline (Fig. 2). The CI declined from 181 ± 30 mL/kg • min at baseline to 128 ± 16 mL/min • kg ($p < 0.05$) at the end of ischemia and to 80 ± 30 mL/min • kg ($p < 0.05$) at the end of the 8-hour monitoring period (Fig. 3). Pulmonary arterial wedge pressure was maintained at baseline levels of 4 mmHg. Physiologic shunt remained unchanged from a baseline value of 5 ± 1%.

The platelet count fell progressively from 133,000 ± 11,000/mm^3 to 93,000 ± 14,000/mm^3 after 4 hours of ischemia and to 38,000 ± 13,000/mm^3 after 4 hours of reperfusion ($p < 0.05$) (Fig. 4). There was no change in In-111 activity in the lungs or legs. The wet/dry weight ratio of the lungs was 5.32 ± 0.12, a value similar to the sham group 5.59. Light microscopy of the lungs revealed accumulations of PMNs throughout the lung paren-

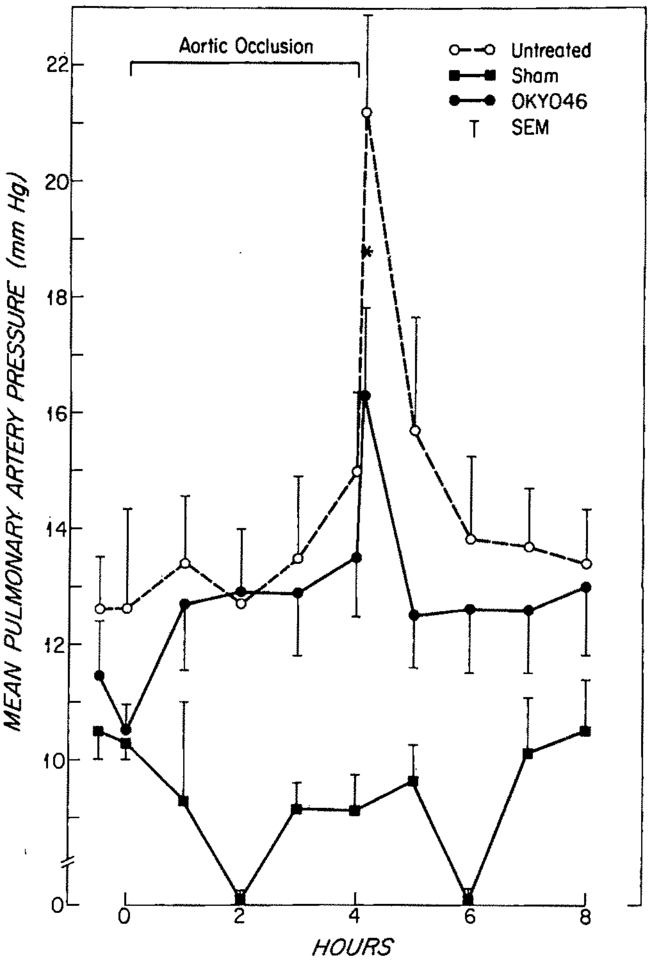


FIG. 2. Release of the aortic clamp led to an immediate rise in MPAP in untreated animals. This increase was blunted by pretreatment with OKY-046. Asterisks (*) refers to significant differences between placebo and OKY-046-treated groups.

chyma (Fig. 5A). Platelet microaggregates were not seen and there was no evidence of vascular congestion. While most leukocytes were seen within vessels, foci of PMNs along with a proteinaceous exudate were present within alveoli. Quantitative PMN counts were 213 ± 34 PMN/25 HPF in dependent and 153 ± 27 PMN/25 HPF in nondependent lung regions (Fig. 6). In contrast, the lungs of sham animals had 100 PMN/25 HPF in dependent and 85 PMN/25 HPF in nondependent regions.

Pretreatment with the Tx inhibitor OKY-046 led to baseline plasma TxB_2 levels of 95 ± 35 pg/mL, a value lower than placebo-treated dogs ($p < 0.05$). In this group there was no ischemia-induced increase in plasma TxB_2 concentration (Fig. 1). The small rise in MPAP from 13 ± 1 mmHg at baseline to 16 ± 2 mmHg after 5 minutes of reperfusion was in contrast to the placebo-treated animals ($p < 0.05$) (Fig. 2). Further, OKY-046 pretreatment led to a higher CI than in the placebo group throughout the 8 hours of monitoring, 216 ± 32 mL/min • kg after 4 hours of ischemia ($p < 0.05$), and 133 ± 40 mL/min • kg ($p < 0.05$) after 4 hours of reperfusion (Fig. 3).

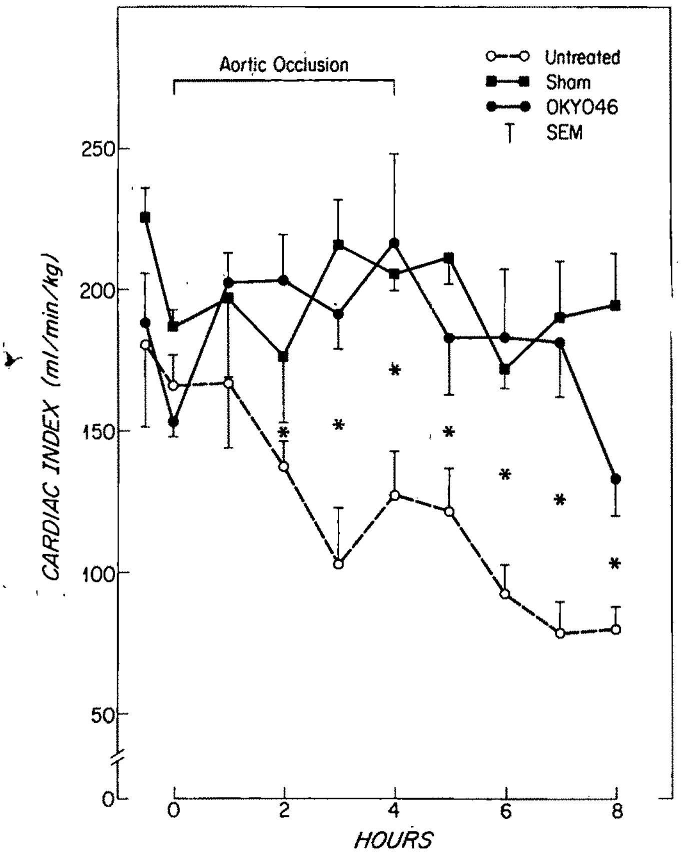


FIG. 3. Cardiac index declined in untreated relative to OKY-046–treated animals. Asterisks (*) refer to significant differences between placebo and OKY-046 treated groups.

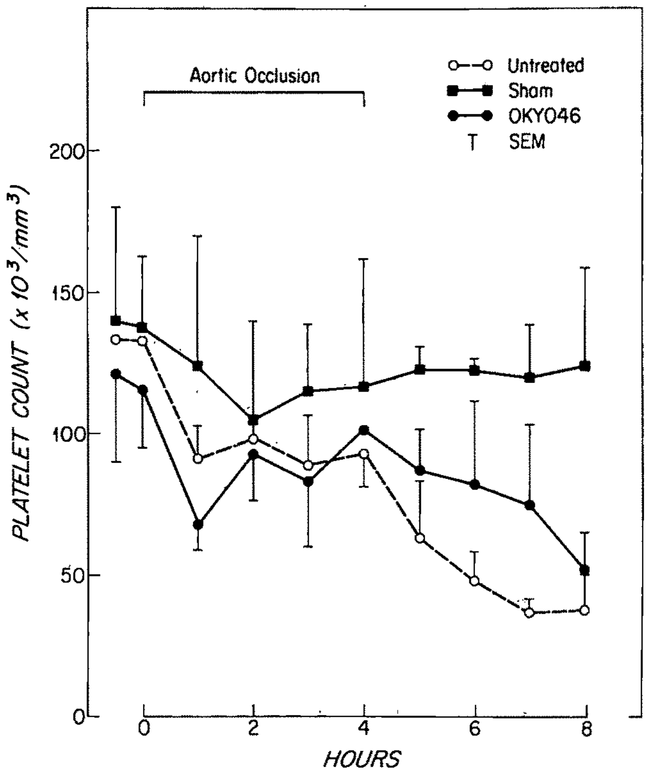
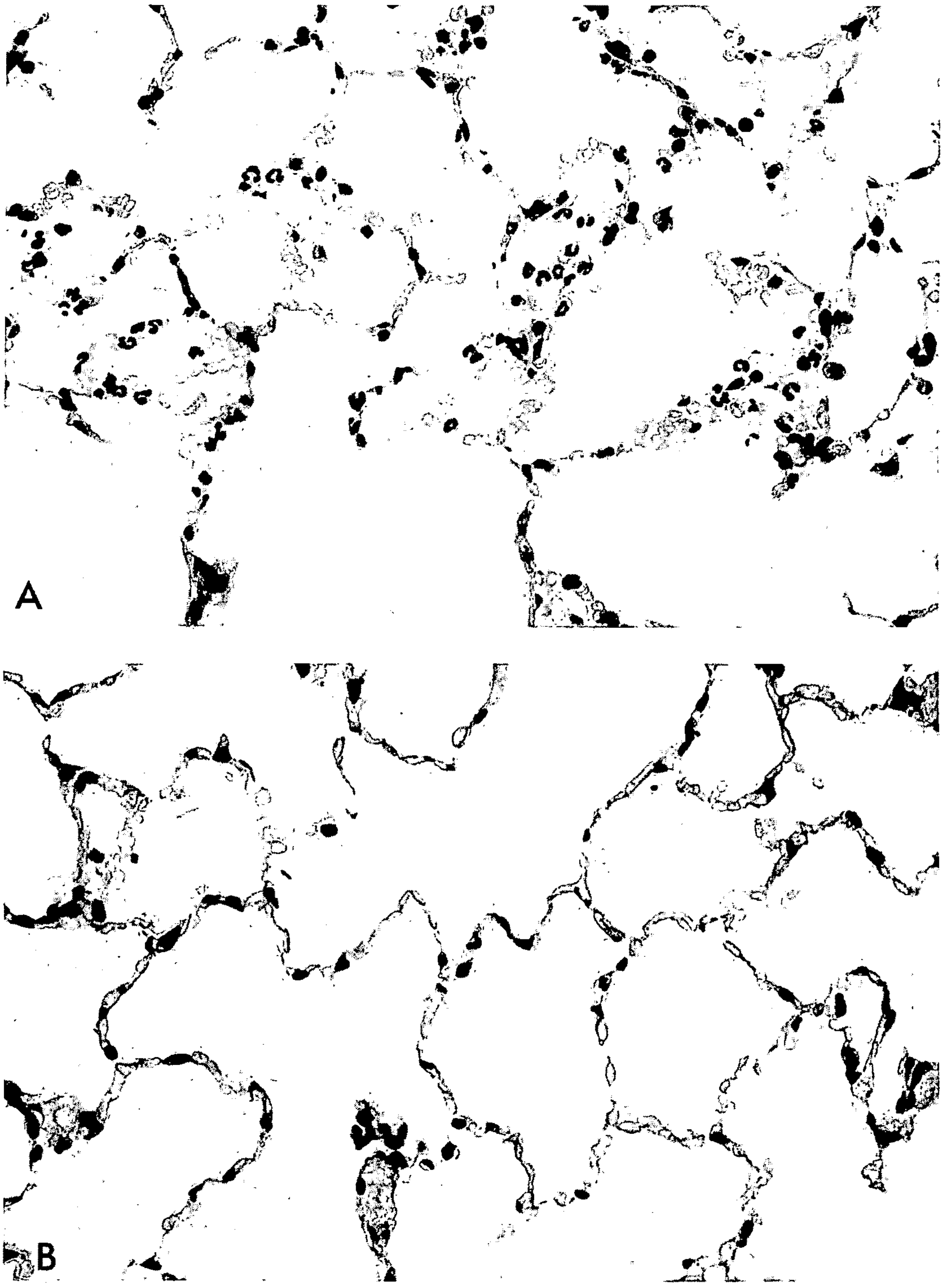


FIG. 4. Platelet counts fell both in untreated and OKY-046–treated groups.

There were no pathologic changes on microscopic examination in OKY-046 pretreatment animals (Fig. 5B). Pulmonary leukocyte counts were lower than placebo-treated animals 127 ± 15 PMN/25 HPF in dependent areas of the lung ($p < 0.05$) and 95 ± 11 PMN/25 HPF in nondependent areas ($p < 0.05$) (Fig. 6). The decline in circulating platelet counts was similar to untreated animals, 121,000 ± 22,000/mm^3 at the end of the ischemic period and 51,000 ± 14,000/mm^3 after 4 hours of reperfusion. Physiologic shunt was unchanged from 6 ± 2% at baseline. Ratio of wet to dry lung weight was 5.36 ± 0.09.

Discussion

Four hours of infrarenal aortic clamping led to a rise in levels of plasma TxB_2 beginning 5 minutes after clamp release but becoming most prominent after 3 hours of reperfusion (Fig. 1). On the other hand, the increase in MPAP occurred just after release of the aortic clamp and was restored to baseline after 3 hours of reperfusion (Fig. 2). The fact that inhibition of Tx synthesis significantly limited the pulmonary hypertension



FIGS. 5A and B. Placebo-treated animals (*A*) showed accumulations of PMNs in capillary beds throughout the lung parenchyma. Most neutrophils were within vessels, but in other fields foci of inflammatory cells and proteinaceous exudate within alveolar air spaces were also present. Pretreatment with OKY-046 led to normal histology without PMN accumulations (*B*).

strongly suggests a direct pulmonary arterial constrictive effect of TxA_2. The observation at 3 hours of reperfusion in saline-treated animals that plasma TxB_2 concentrations continued to rise while MPAP fell does not negate the role of TxA_2. A changing and more remote site of TxA_2 synthesis, an agent with a 30-second half-life, could have altered its biological effect.

Depression of cardiac function has been associated with Tx synthesis.[10-12] The mechanism appears to be indirect. A circulating agent in plasma that depresses contractility of a papillary muscle has been shown to be generated as a consequence of Tx synthesis.[4] The ability to prevent the appearance of this circulating negative inotrope and maintain CI has been described in patients treated with cyclooxygenase inhibitors undergoing abdominal aortic aneurysmectomy. The present data confirm the relationship between the synthesis of Tx and depression of cardiac output.

The consequences of lower torso ischemia are not only pulmonary hypertension and depression of cardiac function but also acute respiratory failure. The original hypothesis proposed to explain pulmonary dysfunction involved the release of microemboli from the ischemic lower extremities.[1-3] Our inability to find evidence of pulmonary platelet sequestration either by In-111 labelling or by microscopy does not confirm this original thesis. In other settings where platelet microemboli were believed to play pathophysiologic roles such as hemorrhagic shock, current evidence also denies their importance.[13]

Leukocyte entrapment in the lungs does not appear to be the result of platelet-neutrophil microembolization. If microaggregates accumulated in the lungs and were dependent on Tx synthesis, this would be at variance with the facts that the observed thrombocytopenia was neither related to platelet sequestration in the lungs nor to Tx synthesis. Thromboxane generation in the lower torso should not be selective in causing PMN and not platelet aggregation and mechanical entrapment in the pulmonary microcirculation.

A more attractive postulate to explain PMN accumulations in the lungs is that TxA_2 acts uniquely with respect to PMN in promoting chemoattraction. Classic chemattractants such as leukotriene (LT) B_4 or complement fragment C5a could be released from the lower torso and stimulate leukocytes as well as lung endothelium to synthesize TxA_2. Such chemoattractants, when applied to endothelium grown in culture, will stimulate Tx synthesis.[14] Further, other work has shown that LTB_4 or C5a can cause PMN accumulations by means of a Tx pathway.[15] One hypothesis to explain PMN accumulations in the lungs is that an agent released from the ischemic lower torso leads to Tx synthesis by leukocytes as well as the pulmonary microvasculature which in return results in endothelial-PMN adherence. A second postulate is that TxA_2 directly influences endothelial cell gap junctions by varying stress fiber assembly. Agents such as Tx that decrease the number of actin cables lead to a widening of interendothelial junctions, thereby allowing increased diapedesis of PMN.[16]

The observation that more PMNs are sequestered in dependent than in nondependent lung regions is likely to be a consequence of the gravitational distribution of blood flow, which favors dependent regions (Fig. 6). The putative circulating mediators that determine pulmonary PMN sequestration are also likely to be distributed to the lungs with regard to blood flow distribution.

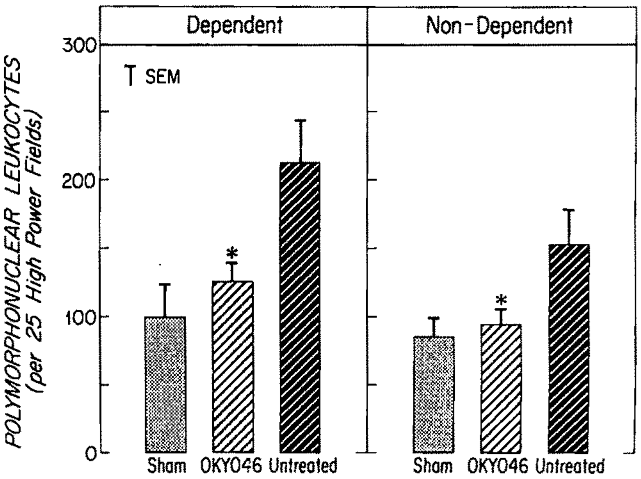


FIG. 6. Leukocytes were unevenly distributed throughout the lung. Increased PMN counts were found in the higher flow-dependent areas compared to the lower flow nondependent areas both in untreated and OKY-046-treated animals. Asterisks indicate significant differences between placebo- and OKY-046-treated groups.

Although pulmonary edema was not documented by an increase in the wet/dry weight ratio of the lungs, there was histologic evidence of early microvascular injury manifest by foci of proteinaceous exudates in alveoli containing inflammatory cells (Fig. 5). These changes were not severe and therefore the maintenance of a low physiologic shunt was not surprising. It is possible that the pulmonary injury would have worsened with time and the passage of more PMNs into the extravascular spaces. It is generally believed that PMNs are the responsible agents for most varieties of acute respiratory failure.[16,17]

In summary, lower torso ischemia led to the generation of TxA_2 which is responsible for the pulmonary hypertension, cardiac depression, and pulmonary PMN accumulations noted following aortic clamp release and reperfusion.

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The Selective Use of Antilymphocyte Serum for Cyclosporine Treated Patients with Renal Allograft Dysfunction

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Eighty-seven adult renal allograft recipients were initially treated with cyclosporine-prednisone immunosuppression. Thirty patients experienced no episode of rejection. Antilymphocyte antibody therapy (ALS) was administered to 21 of the 68 recipients of cadaveric donor allografts for either primary allograft dysfunction or acute rejection, and to 6 of 19 recipients of haploidentical, living-related allografts because of steroid-resistant rejection. The cumulative allograft and patient survival for the entire series (follow-up 9–36 months) was 84% and 95%, respectively. This improvement in the rate of successful transplantation can be attributed to the selective addition of ALS therapy to recipients with specific instances of renal allograft dysfunction. In this report, the indications for the use of ALS preparations following prophylactic CsA immunosuppression are reviewed. Experience with the protocols of the ALS administration is also discussed. In selected cases, the administration of either ATG or OKT3 can significantly benefit CsA recipients who experience either primary allograft nonfunction or an epidose of acute rejection.

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DESPITE THE IMPROVEMENT in renal allograft survival in patients receiving cyclosporine (CsA) immunosuppression, a significant proportion of these recipients still experience rejection episodes, some of which are unresponsive to high-dosage steroids. This is reflected in the current survival statistics, which note a first-year renal allograft loss of approximately 25 to 30% in several CsA multicenter trials.[1–3] At least half of these allograft losses were due to rejection. Whereas the role of additional immunosuppressive therapy such as antilymphocyte serum (ALS) has been well defined for patients receiving azathioprine-prednisone immunosuppression, its proper use in CsA-treated patients has been less certain. Early reports of experimental trials using CsA in combination with ALS in nonhuman primates suggested that unacceptable complications might be experienced in patients receiving CsA and ALS concomitantly.[4] Thus, clinicians have been appropriately cautious about administering CsA and ALS in a combined regimen.

During the past 3 years, CsA has been routinely administered at the Massachusetts General Hospital as the primary immunosuppressive medication for recipients of both cadaveric donor (CD) and haploidentical living-related donor (LRD) renal allografts. Our experience has suggested that the rate of successful renal transplantation reported in the above noted multicenter trials can be improved even further by adding ATG or OKT3 antilymphocyte preparations to CsA protocols for selected instances of renal dysfunction. This report details our experience with the administration of antilymphocyte antibody preparations in CsA-treated renal allograft recipients and our current recommendations for their use in these patients.

Methods

Between January 1984 and April 30, 1986, 87 consecutive adult renal allograft recipients were treated with CsA-prednisone immunosuppression (Table 1). Sixty-eight patients were recipients of CD allografts and 18 received haploidentical LRD allografts. One HLA-identical LRD recipient was treated with CsA-prednisone because he had received a second renal allograft. One patient suffered loss of a CD allograft because of a donor-transmitted bacteroides infection. This patient was included in the statistical failures of CD allografts. No patient was excluded from this retrospective review.

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TABLE 1. *Characteristics of 87 Consecutive Adult Renal Allograft Recipients*

	LRD	CD
Donor	19	68
Primary transplant	18	60
Secondary transplant	1	8 (10%)
Diabetics	4	9 (15%)
>50 years age	2	21 (26%)
>50% sensitized	—	26 (38%)
+ Historical crossmatch	—	6

The patient population of this series included diabetics (15%), highly sensitized individuals (38%), recipients over age 50 (26%), and recipients who had previously rejected a primary allograft (10%) (Table 1).

The oral preparation of CsA was administered on a twice daily schedule. The first 40 patients were treated with an initial dosage of 15–17 mg/kg/day. Subsequently the starting dosage has been reduced to 12 mg/kg/day. No patient received intravenous CsA. The CsA dosage was gradually tapered, usually beginning on the 6th or 7th post-transplant day, in an attempt to maintain a plasma level of 50–100 ng/mL measured by radioimmunoassay. The CsA-Radioimmunoassay kit was provided by Sandoz Pharmaceuticals, Basle, Switzerland, for the determination of CsA plasma levels twice weekly.

All recipients were treated with the following steroid protocol administered as prednisone orally or methylprednisolone intravenously. An initial divided dose of 200 mg was given on the day of renal transplantation. The daily dosage was then reduced by 40-mg decrements to 20 mg/day by the 5th day following transplantation. Prednisone dosage was tapered to 15 mg/day approximately 6 weeks following transplantation.

Protocol for Renal Allograft with Primary Function Followed by Acute Rejection

When rejection was suspected, the patient was initially treated with intravenous methylprednisolone (500 mg). The CsA dosage was reduced concomitantly if the plasma CsA level was greater than 150 ng/mL. If the creatinine continued to rise after 48 hours, despite a second pulse of steroids, a percutaneous biopsy was performed. The features of acute rejection associated with CsA immunosuppression have been detailed.[5] The most consistent finding of rejection is not only the presence of mononuclear cells within allograft interstitium, but the penetration of lymphocytes into and through vessel walls with some being characteristically attached to the arteriole endothelium. This finding of endothelialitis is the signal feature that distinguishes rejection from CsA nephrotoxicity.[5]

Biopsy confirmation of persistent rejection (that is failure to improve or reverse with at least two doses of methylprednisolone) prompted the initiation of antilymphocyte antibody therapy. Either OKT3 5 mg/day (Orthoclone, Ortho Pharmaceutical Company, Raritan, New Jersey) was administered *via* a peripheral vein for 10 consecutive days, or ATG 15 mg/kg/day (ATGAM, Upjohn Company, Kalamazoo, Michigan) was administered through a central vein or A-V fistula for 10–14 days. In the initial seven CsA patients treated with OKT3, and CsA dosage was maintained at the pre-OKT3 dose throughout the course of OKT3 treatment. However, in more recent patients, the CsA dosage was reduced to 2–3 mg/kg/day during OKT3 therapy. Following completion of OKT3 treatment the CsA dose was increased to 4–6 mg/kg/day. In all of these patients with "steroid-resistant" rejection, azathioprine (2 mg/kg/day) was begun on the 7th day of OKT3 treatment and continued indefinitely. Subsequent rejection episodes following withdrawal of OKT3 therapy were treated initially with methylprednisolone (500 mg IV). If biopsy-confirmed rejection failed to reverse after 2 bolus doses, ATG was then administered daily for 10–14 days. During ATG therapy, CsA dosage was reduced to 2–3 mg/kg/day and azathioprine was reduced to 25–50 mg/day. Allograft failure was defined as return to dialysis or patient death.

Protocol for Renal Allograft with Primary Dysfunction

The CsA dose was reduced to 6–8 mg/kg/day for the first 3 days following transplantation. Patients whose allograft function recovered sufficiently to allow withdrawal of dialysis by this time were then treated as outlined in Figure 1. ATG was added only if dialysis was required beyond this period. Azathioprine (2 mg/kg/day) was substituted for CsA during the period of ATG administration. When diuresis (greater than 1000 mL/day) and a falling creatinine allowed withdrawal of dialysis support, ATG was discontinued and CsA was resumed at a reduced dose (4–6 mg/kg/day). Azathioprine was not discontinued in these patients who then were maintained on triple drug therapy.

Protocol for Conversion of CsA to Azathioprine in Long-term Patients

At 6–12 months following transplantation, recipients of renal allografts during 1985–1986 with stable allograft function were randomized to either CsA withdrawal or to triple drug therapy. Azathioprine (2 mg/kg/day) was added to the regimen of all patients not yet receiving the drug for 1 week without altering the CsA dose. During the subsequent week the CsA dosage was decreased by 50%. CsA was then either discontinued (in half of the patients) or it was continued at the reduced level (in the other randomized half). No changes were made in the prednisone dose during or following CsA alteration.

Results

Comparison to a group of renal allograft recipients treated previously in this unit with azathioprine, prednisone, and ALS immunosuppression emphasizes the improvement that has been achieved with the CsA therapeutic protocols. The actual 1-year survival for 64 recipients of CD renal allografts treated during 1982 and 1983 (prior to CsA availability) was 65%. In contrast, the actual allograft survival is 85% (Table 3) for the 60 CsA-treated CD renal allograft recipients who have been followed for at least 12 months following transplantation. With a follow-up of 9–36 months, the cumulative allograft survival for the entire series of 87 patients is 84% (73/87). Nine allografts were lost to rejection, one was lost to donor bacteroides infection, and four others have been lost at the time of patient death. The etiology for the four patient deaths was as follows: viral pneumonia (6 months), a preforated peptic ulcer (12 months), amyloid hepatic failure (18 months), and a myocardial infarction (27 months).

Despite the excellent long-term prognosis for CsA-treated patients, acute rejection episodes were diagnosed in 45 of 68 CD recipients and 12 of 19 LRD recipients. These usually occurred during the first month following transplantation, after which documented episodes of rejection were infrequent. All rejection episodes were initially treated with additional doses of Solu-medrol®. However, 14 CD allograft recipients and six LRD recipients (35%) subsequently required antilymphocyte antibody treatment for steroid-resistant rejection. Seventeen of these patients had biopsy-confirmed rejection. CsA toxicity was excluded in each of these patients. Fourteen of this group received OKT3; the remainder received ATG. Although the rejection episode for which ALS was added was reversed in each of these patients, 12 of them developed later rejection episodes. In nine patients the subsequent episode of rejection was irreversible despite high-dosage steroids and/or further ATG therapy. Four of this refractory group were recipients of OKT3 who were subsequently treated with a 7–10—day course of ATG. No patient received two courses of OKT3 therapy. Nevertheless, the kidneys of 11 of these 20 patients were salvaged by antilymphocyte therapy, thus reducing in half the allograft loss to steroid-resistant rejection. Six of these patients are currently on triple drug therapy initiated after ALS treatment.

In the initial seven CsA-treated patients given OKT3 for acute rejection, the CsA dose was intentionally maintained at the pre-OKT3 level in order to exclude the possibility that subsequent improvement in allograft function might have resulted from manipulation of CsA levels. Six of these patients had rejection confirmed by biopsy. No CsA toxicity was evident. Although all patients responded to OKT3 treatment, the mean creatinine at completion of OKT3 therapy was 2.5 mg/dL. In contrast, in our previous experience with OKT3 therapy in azathioprine-treated patients we had routinely achieved a creatinine of less than 1.5 mg/dL. This observation has led us to conclude that occult CsA nephrotoxicity may irreversibly injure the allograft during periods of serious rejection. Therefore, we currently withdraw CsA during ALS treatment for severe rejection (Fig. 1).

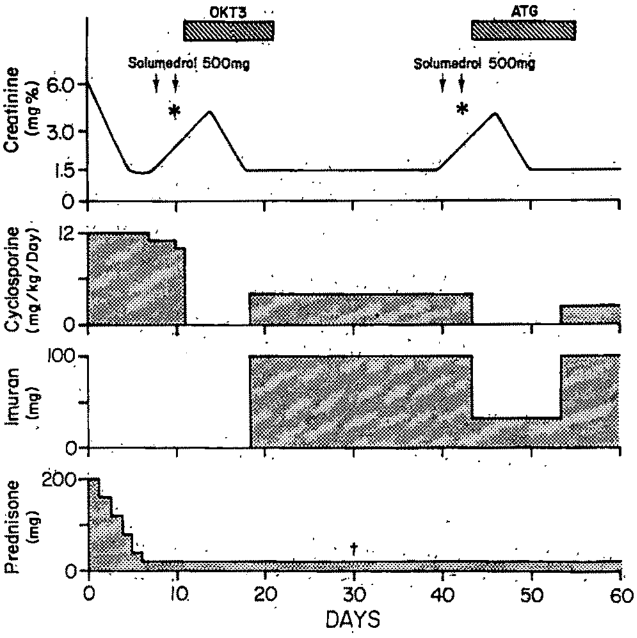

FIG. 1. Current therapeutic plan for patients with renal allograft with primary function followed by acute rejection. *Renal allograft biopsy; †patients with stable renal function and no episode of rejection would reduce their prednisone dose to 15 mg/day at 4–6 weeks following transplantation.

The incidence of early renal dysfunction requiring dialysis in CD allograft recipients in this series was 14.7% (10/68). All of these allografts recovered satisfactory function by 14 days following transplantation. In five patients CsA was discontinued between 3 to 12 days following transplantation (Table 2). ATG was administered daily during this period (8–14 doses). In the other five patients CsA was continued at a reduced dose (6 mg/kg/day), with two also receiving ATG during the first 2 weeks following transplantation. Although several of these patients were either highly sensitized or the recipients of a second allograft, no evidence of hyperacute or accelerated rejection was implicated in the initial episode of dysfunction. No recipients of LRD allografts

TABLE 2. *Results*

	LRD	CD
Primary allograft dysfunction	0	10/68 (14.7%)
CsA discontinued	—	5
ATG required	—	7
Actual allograft survival (1 year)	—	9/10 (90%)
No rejection	7/19 (36.8%)	23/68 (33.8%)
Rejection therapy		
Methylprednisolone only	6	31/45 (68.8%)
OKT3	4	10
ATG	2	4
Actual allograft survival (1 year) post OKT3 or ATG therapy	3/6 (50%)	7/14 (50%)
Actual survival (1 year)	15 patients	60 patients
Patient	15/15 (100%)	58/60 (96%)
Allograft	12/15 (80%)	51/60 (85%)
Cumulative allograft survival (9–36 m)	16/19 (84.2%)	57/68 (83.8%)

required hemodialysis because of primary allograft dysfunction.

Withdrawal of CsA was attempted in 40 recipients with stable renal function for at least 6 months following transplantation. Twenty-five of these patients (allograft recipients during 1984) had undergone CsA withdrawal prior to the randomized study. Since 1985, 15 patients have randomized to CsA withdrawal. Thirteen of the total group of 40 patients (32.5%) developed acute rejection beginning between 2 weeks and 6 months following CsA withdrawal. Treatment with intravenous methylprednisolone (500 mg) in all patients plus resumption of CsA (11/13) successfully reversed these late rejection episodes. Nevertheless, one patient died of complications related to a perforated peptic ulcer that developed in association with the increased steroid dosages. Since 1985, 14 other recipients were randomized to triple drug therapy as described in the Methods section. One of these patients required OKT3 treatment of acute rejection 3 months following the addition of azathioprine. None of the other triple drug patients has experienced an episode of rejection.

Discussion

Disagreement persists among transplant groups as to what role antilymphocyte antibody therapy should play in the immunosuppressive protocols of CsA-treated allograft recipients.[6] Recommendations range from proposals that ALS be given to every patient[7,8] to the caution that the two agents may produce overimmunosuppression if used together.[9] Our observations in 87 consecutive adult renal allograft recipients have led us to a selective approach with which the obvious benefits of ALS therapy are achieved, but which exposes only about 30% of patients to possible complications of an admittedly more intensive regimen. Thus, on the basis of this experience, we recommend the following ALS protocols (detailed in Fig. 1 and Table 3) for the CsA-treated patient: (1) ATG or ALG should be given and CsA discontinued in patients whose primary allograft dysfunction persists beyond 3 days; (2) OKT3 therapy should be reserved for primary episodes of acute rejection that are unresponsive to at least two boluses of IV methylprednisolone; (3) ATG may be employed for subsequent episodes of rejection that may occur following OKT3 withdrawal; and (4) the CsA dosage should be greatly reduced or even discontinued during periods of ALS therapy. These protocols of immunosuppression more precisely define the indications for ALS administration following CsA treatment and the appropriate use of currently available monoclonal and polyclonal preparations. Not all renal allograft recipients with primary allograft dysfunction or acute allograft rejection require ALS treatment. Approximately 70% of the renal allograft recipients in this series had uncomplicated postoperative courses and were successfully managed with CsA-steroid immunosuppression alone. This level of success is similar to the survival rates reported previously in multicenter trials.[1–3] With the selective addition of ALS therapy to the immunosuppressive protocols of the remaining subsets of patients (70% of patients with primary allograft dysfunction and 33% of patients with steroid-resistant rejection), we have achieved further improvement in allograft survival.

We have used ATG for prophylactic immunosuppression if necessary during early periods of allograft dys-

TABLE 3. *Current Protocol for Renal Allograft Recipients with Primary Dysfunction*

Day	Dialysis	CsA Dose (mg/kg/day)	Prednisone	ATG	Imuran (mg)
0		12	200	–	–
1–3	+	6	160–120	–	–
4	+	0	40	15 mg/kg/day	25–50
5–14	+	0	20	+	25–50
	–	4–6	20	–	75–100

function and reserved the use of OKT3 for episodes of steroid-resistant rejection, since many patients develop anti-idiotypic antibodies following initial treatment with OKT3.[10] The recommendation to withhold ATG or ALG for 72 hours following transplantation is based on our observation that 30% of patients who experienced primary dysfunction regained satisfactory function without ATG. Our approach has been to reduce the CsA dose for the first 3 days of dysfunction. If dialysis is still necessary at this time, the CsA is discontinued and ATG is begun (Table 3). Continuing CsA at reduced dosages for 72 hours has had no apparent adverse effect on the eventual resumption of allograft function, providing that CsA plasma levels were maintained in therapeutic range. Only five of the ten patients with primary dysfunction in this series had their CsA discontinued, and all of these allografts resumed function by 12 days following transplantation.

Because of the increased risk of nephrotoxicity and untoward hemodynamic effects following IV administration of CsA,[11] we do not use the parenteral preparation for renal allograft recipients. All patients, including diabetics, children, and even recipients who have undergone simultaneous bilateral nephrectomy, have been able to tolerate the oral preparation within 12 hours of operation.

In CsA-treated patients whose allografts function well immediately following transplantation, we have observed that the serum creatinine generally plateaus between 1.5 and 2.5 mg/dL at 7–10 days. In most patients persistent tapering of the CsA dose to maintain plasma levels of no greater than 150 ng/mL is required to achieve this level of function. In some patients significant nephrotoxicity is still encountered despite plasma levels in the 50–150 ng/mL range, and further reduction in CsA dosages is mandated, particularly if there are other signs of CsA toxicity such as hypertension and hyperkalemia (coincident with satisfactory urine output).

Subsequent deterioration in renal function usually indicates rejection. However, if the CsA level is greater than 150 ng/mL, the dosage is reduced further and, as noted in our rejection protocol (Fig. 1), a single dose of methylprednisolone has generally been administered. Continuing deterioration in renal function despite these measures necessitates a second bolus of IV methylprednisolone and usually a renal allograft biopsy. We have used the determination of acute rejection by biopsy and the failure to respond to bolus doses of methylprednisolone as the indication for administration of OKT3.

Thus far, all of the CsA-treated patients who have received OKT3 for a primary episode of rejection have experienced successful reversal. Although OKT3 therapy is as effective in CsA-treated patients as in those receiving azathioprine, CsA toxicity appears to exacerbate the dysfunction associated with a rejection episode. This became apparent in our first seven OKT3-treated patients in whom the CsA dosage was deliberately maintained at the prerejection level. Despite improvement in allograft function following OKT3 treatment, the serum creatinine fell only to a mean of 2.5 mg/dL, suggesting unremitting CsA toxicity. Our current approach is to discontinue CsA during OKT3 treatment (Fig. 1) as we rely on the OKT3 and a modest dose of prednisone to achieve sufficient immunosuppression. This policy is designed to avoid the long-term renal damage that we now suspect develops when rejection occurs in patients who simultaneously suffer from CsA nephrotoxicity. Thistlethwaite and colleagues have also considered that CsA nephrotoxicity may occur in some of their OKT3-treated patients, and they too have adopted a protocol involving CsA omission during OKT3 therapy.[12]

The addition of azathioprine at 7 days following the onset of OKT3 therapy is intended to reduce recurrent episodes of rejection in the CsA recipients who have already manifested steroid-resistant rejection. Subsequent rejection episodes in OKT3-treated recipients are initially treated with increased steroids. If continued evidence of biopsy-confirmed rejection is observed, ATG therapy is instituted. ATG rather than OKT3 has been selected in this circumstance because host anti-idiotypic antibodies to the OKT3 molecule, which often develop within 10 days of the initial OKT3 administration, neutralize the effective use of the monoclonal antibody.[10] However, if ATG has been administered for the primary episode of acute rejection, OKT3 may be given for the treatment of a subsequent rejection episode.

Similar to the experience of Morris and Tilney,[13,14] approximately 30% of our recipients were noted to have an episode of rejection following attempted withdrawal of CsA in the late post-transplant period, even though renal function had been stable for at least 6 months. Furthermore, we have noted that rejection can occur several months following CsA withdrawal, when one might have considered the patient to be beyond jeopardy. Treatment has routinely consisted of methylprednisolone and the necessity for ALS treatment has been rare. However, most of these patients have resumed CsA treatment indefinitely. We are currently conducting a randomized trial to determine whether it is more beneficial to remain on triple drug therapy *versus* attempting to withdraw CsA. Although the triple drug patients in this series have initially experienced less rejection following randomization, we are continuing the study because the long-term outcome of CsA therapy is unknown and the financial burden of CsA for many of our patients remains significant.

In our experience, the risk of infection following the concomitant administration of ATG to CsA-treated patients and the sequential administration of ATG and OKT3 to only a selected group of CsA patients has been minimal. As suggested by the 96% patient survival rate at 1 year, the 87 patients in this series experienced no increased risk of viral or opportunistic infection when compared to renal allograft recipients receiving azathioprine-prednisone-ALS immunosuppression.[15] We attribute this low incidence of infection to the markedly reduced daily dose of prednisone and the reduced dose of CsA that has been administered prophylactically and during ALS treatment. We have previously reported that ALS therapy can be used safely and effectively provided the dosage of other immunosuppressive medications is reduced during the period of ALS treatment.[16]

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Alleviation of Cyclosporine Nephrotoxicity with Verapamil and ATP-$MgCl_2$

Mitochondrial Respiratory and Calcium Studies

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Although recent studies have shown that combined treatment with verapamil and ATP-$MgCl_2$ (ATP) prevents cyclosporine (CyA)-induced nephrotoxicity, the mechanism of these effects remains unknown. To study this, rat kidneys were perfused at 100 mmHg for 100 minutes with Krebs buffer containing 7.5 g/dL of albumin and substrates. After an equilibration period of 30 minutes, 500 ng/mL CyA was added. In some experiments 1 μg/mL verapamil was added 10 minutes prior to CyA and in others 2 mM ATP was added to CyA. At the end of the perfusion, cortical mitochondria (mito) were isolated and mito Ca^{2+} and Mg^{2+} (μmoles/g protein) and respiratory control ratios (RCR) were measured. In addition, total tissue Ca^{2+} and Mg^{2+} levels were measured. The results indicate that CyA treatment leads to an accumulation of mito Ca^{2+} and a decrease in ADP/O ratio. Simultaneous administration of ATP with CyA led to an increased mito Ca^{2+} accumulation and depressed RCR, which were corrected by verapamil pretreatment. The combination of verapamil pretreatment and ATP cotreatment with CyA increased tissue ATP levels from 0.8 ± 0.4 (control) to 1.4 ± 0.1 μmol/g. This pharmacologic regimen may prevent CyA-induced nephrotoxicity by preventing mito Ca^{2+} accumulation and by preserving mitochondrial respiratory function. This allows a more efficient generation of ATP and consequently preservation of renal function.

CYCLOSPORINE (CYA) IS A potent inhibitor of lymphokine generation by T-helper cells that allows the survival of allografts without significant myelotoxicity. The main side effect, which limits the usefulness of CyA, has been the drug-induced nephrotoxicity that occurs frequently and is often difficult to distinguish from allograft rejection. The main impetus by researchers in this field has been twofold: (1) to develop a reliable animal model by which to analyze the pathophysiology of CyA nephrotoxicity under controlled and reproducible conditions, and (2) to use the model to investigate the effectiveness of combination pharmacologic drug regimens on the alleviation of renal dysfunction associated with cyclosporine.

We have recently reported[1,2] on a model of CyA nephrotoxicity using an isolated, perfused rat kidney preparation. Addition of CyA to the perfusing solution resulted in oliguria, a reduction in glomerular filtration rate and renal perfusate flow, and impairment of tubular reabsorption of protein, salt, and water compared to the CyA-vehicle-only control group. These early studies also demonstrated that pretreatment with verapamil, a calcium channel antagonist, and cotreatment with ATP-$MgCl_2$ could significantly reduce the nephrotoxic potential of CyA.

The aim of this study was to examine the morphology and mitochondrial function of these CyA-treated kidneys in an attempt to further characterize this acute, *in vitro* model of CyA nephrotoxicity and to study possible mechanisms for the beneficial effects of verapamil and ATP-$MgCl_2$. The results presented will show that an *acute* model of CyA nephrotoxicity can be derived using the isolated perfused rat kidney, which has functional, histologic, and mitochondrial properties similar to that seen clinically. The studies will also suggest that the combination of verapamil pretreatment and ATP-$MgCl_2$ cotreatment with CyA is successful in reducing the nephrotoxic potential of this immunosuppressive agent by preventing mitochondrial calcium accumulation, and by providing a more efficient generation and translocation of ATP.

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Methods

Isolated Perfused Rat Kidney Preparation

Male Holtzman rats (300 g) were used as kidney donors for the isolated perfused kidney preparation. They were fasted overnight but allowed free access to water. The rats were anesthetized with sodium pentobarbital (50 mg/kg, IP) prior to experimentation.

The procedure for kidney isolation was the same as that described in detail previously.[1-7] The abdominal cavity was exposed and the right ureter cannulated with heparinized PE-10 tubing. After systemic heparinization (500 U/kg body weight IV), the right renal artery was cannulated with an 18-g needle *via* the superior mesenteric artery. Perfusion is immediately begun from a gravity resrevoir so as not to interrupt flow to the kidney and to wash the renal vessels of blood. The kidney was then freed from the animal and perfused in a closed circuit perfusion system at 37 C. A mean renal arterial pressure of 90 mmHg was maintained with a nonpulsatile rotary pump and perfusate flow was continuously monitored by a Brooks flowmeter in series with the arterial cannula.

The perfusate consisted of a Krebs-Henseleit bicarbonate buffer solution containing 7.5 g/dL bovine serum albumin, Fraction V (Miles Laboratory, Elkhart, IN), 0.1 mg/mL glucose, 0.5 mg/mL creatinine, and a mixture of amino acids.[8]

Experimental Protocol

After an initial 10-minute equilibration followed by two 10-minute control clearance periods, either 500 ng/mL CyA or the CyA vehicle cremophor EL (BASF, Parsippany, NJ) was added to the perfusate. In some experiments 2 mM ATP-$MgCl_2$ (*i.e.*, 2 μmol/mL) was added simultaneously with CyA, whereas in others 1.0 μg/mL of verapamil was added 10 minutes prior to CyA. In the third group of experiments, the combination of 1.0 μg/mL verapamil pretreatment and 2 mM ATP-$MgCl_2$ cotreatment with CyA was studied. Kidneys were perfused for a total of 100 minutes and perfusate and urine samples were collected at 10-minute clearance intervals.

Mitochondrial Studies

At the end of experimentation, mitochondria were isolated as described by Wilson et al.[9] Briefly, the cortex was separated from the inner white medulla and capsule and immersed immediately in a chilled solution containing 210 mM mannitol, 70 mM sucrose, 0.1 mM EGTA, 0.5% bovine serum albumin, and buffered to 7.4 pH with 2 mM K-HEPES. The tissue was homogenized in the above buffer, centrifuged at 4 C twice, and the supernatant discarded. The mitochondrial pellet was resuspended in the 70-mM sucrose solution at 100 mg protein/mL. Protein content was determined by the Bio Rad protein assay.[10]

Recovery rate of mitochondria in *in vivo* and *in vitro* kidney preparation were similar and in the different experimental groups were also comparable (approximately 10–11% total mitochondria protein per mg of original kidney weight). Contamination of the mitochondrial preparation by endoplasmic reticulum during the isolation procedure was assessed by measurement of glucose 6-phosphatase, an endoplasmic reticulum marker.[9] There were minimal amounts of endoplasmic reticulum in the *in vivo* compared to *in vitro* renal mitochondria isolates, with the ratio of total cellular to mitochondrial pellet glucose 6-phosphatase activity being 31.3 *versus* 36.0 ($p > 0.05$), respectively.

Mitochondrial O_2 consumption was measured with a YSI O_2 monitor (Yellow Springs Instruments, Yellow Springs, OH) equipped with a Clark-type electrode and a temperature-regulated water bath. The reaction mixture contained 120 mM KCl, 2 mM phosphate, 4 uM rotenone, and 1 mM EGTA buffered with 5 mM Tris-HCl, pH 7.1. After equilibration of the mixture at 25 C, mitochondria (2–4 mg of protein) were added and the rate of oxygen consumption measured after addition of 5 mM K-succinate. State 3 respiration was initiated by addition of a phosphate acceptor (300 μmoles of ADP) and state 4 respiration was measured after all the ADP had been exhausted to ATP. The respiratory control ratio (RCR) is calculated as the ratio of O_2 consumption in the presence (state 3) and absence (state 4) of ADP and is a measure of the integrity of the mitochondrial preparation. The efficiency of phosphorylation is calculated from the oxygen trace and is equal to the ratio of the known amount of ADP added to the amount of oxygen consumed during the burst of the state 3 respiration. This approaches 2 with succinate as the substrate in mitochondria that exhibit high respiratory control. The maximal rate of O_2 consumption was measured after the addition of an uncoupler of oxidative phosphorylation, 0.2 μmoles FCCP (carbonyl cyanide p-trifluoro methoxypenyl hydrasone, Sigma Chemical Corp., St. Louis, MO).

Mitochondrial and tissue Ca^{2+} and Mg^{2+} were determined by atomic absorption (Perkin Elmer, Norwalk, CT). The isolated mitochondria (5 mg protein) were digested overnight in 200 μL nitric acid and then diluted in 5 mL deionized water prior to measurement while the tissue calcium and magnesium was determined from the initial cortical homogenate.

TABLE 1. *Mitochondria and Tissue Calcium and Magnesium Levels in Isolated Kidneys Treated with Cyclosporine, ATP-MgCl$_2$, and Verapamil*

	In Vivo Control (N = 4)	*In Vitro* Control (N = 4)	*In Vitro* CyA (N = 4)	*In Vitro* CyA + ATP (N = 4)	*In Vitro* CyA + V (N = 4)	*In Vitro* CyA + ATP + V (N = 4)
Ca^{2+}						
Mitochondria (μmol/g protein)	31.5 ± 5.2	33.1 ± 3.2	40.2 ± 6.1*	65.6 ± 11.1*†	32.4 ± 1.1†	38.3 ± 5.7
Tissue homogenate (μmol/g protein)	11.8 ± 1.8	11.9 ± 1.6	13.4 ± 2.8	23.2 ± 8.5*†	10.2 ± 0.8	8.7 ± 0.7†
Mg^{2+}						
Mitochondria (μmol/g protein)	33.0 ± 4.1	25.7 ± 5.9	27.2 ± 3.6	43.9 ± 2.1*†	32.6 ± 2.5	42.1 ± 8.8*†
Tissue homogenate (μmol/g protein)	40.5 ± 8.0	34.6 ± 6.1	34.5 ± 4.6	43.8 ± 4.5	36.0 ± 1.8	32.3 ± 6.0

Rat kidneys were isolated and perfused *in vitro* with a modified Krebs HCO$_3$ buffer containing CyA, verapamil, and ATP-MgCl$_2$. After 100 minutes of perfusion, kidney cortex was separated from capsule and white medulla, homogenized (tissue homogenate), centrifuged, and the supernatant discarded. The pellet (mitochondria) was washed twice and resuspended in 70 mM sucrose. Ca^{2+} and Mg^{2+} were determined by atomic absorption. For details see Methods. Values are expressed as means ± SE, N = number of kidneys; CyA = cyclosporine; ATP = ATP-MgCl$_2$; V = verapamil.

* $p < 0.05$ compared with *in vitro* control.

† $p < 0.05$ compared with CyA.

Morphologic Studies

At the end of experimentation in some kidneys, a fixative consisting of 0.067M cacodylic acid, pH 7.4, 0.8% paraformaldehyde, 1.25% glutaraldehyde, and 0.01% CaCl$_2$, was allowed to perfuse the kidneys by gravity. A total of 300–400 mL of fixative was used in each kidney. Cortical slices of kidney were minced and placed in 0.2 M cacodylate buffer, pH 7.4 containing 8% dextrose for 1 hour. The tissue was then postfixed in 2% osmium tetroxide, dehydrated and epon embedded, sectioned with a diamond knife, and stained with uranylacetate and lead citrate. The sections were viewed in a Phillips 201 electron microscope. A total of three sections from a minimum of two different blocks from each of three rats per group was examined.

Statistical Analyses

Statistical analyses were performed by Student's t-test and ANOVA where applicable. Values of p less than 0.05 were considered statistically significant. Values are expressed as means ± standard error of the mean.

Results

Mitochondrial Studies

Table 1 shows that the CyA-treated kidneys had a small but significant mitochondria calcium accumulation compared to the control kidneys. This mitochondrial calcium loading was exacerbated by ATP-MgCl$_2$ treatment but prevented in both the CyA and the CyA + ATP-MgCl$_2$ group by verapamil pretreatment. Tissue calcium was unaffected by CyA treatment, but this rose with the addition of ATP-MgCl$_2$. This increased tissue calcium with ATP-MgCl$_2$ could be prevented by verapamil pretreatment. Mitochondrial and tissue magnesium levels were unchanged with CyA treatment. However, this increased in the kidneys treated with ATP-MgCl$_2$ and was not reversed by verapamil treatment. Further studies have shown that this increase is probably due to the MgCl$_2$ carrier since this finding could be reproduced with MgCl$_2$ treatment alone but not with ATP alone (unpublished observations).

Table 2 shows that cortical mitochondria from kidneys treated with CyA did not show any significant difference in state 3, state 4, or uncoupled oxidative phosphorylation compared to the control group. There was, however, a small but significant decrease in ADP/O ratios in the mitochondria isolated from CyA-treated kidneys. The ATP-MgCl$_2$ cotreated group and the verapamil pretreated group showed a significant loss of respiratory phosphorylative activity (state 3) and RCR compared to the control and CyA-treated groups. In addition, the verapamil pretreated group had a lower uncoupled oxidative phosphorylative activity. The combined treatment with verapamil, ATP-MgCl$_2$, and CyA restored mitochondrial respiratory activity to normal.

Renal Ultrastructure

There were no consistent histologic abnormalities seen in the glomerulus, arterioles, or distal tubular cells of the CyA-perfused kidneys. There were, however, TABLE 2. *O_2 Consumption in Mitochondria Isolated from Rat Kidneys Treated with Cyclosporine, ATP-$MgCl_2$, and Verapamil*

	In Vivo Control (N = 4)	*In Vitro*				
		Control (N = 4)	CyA (N = 4)	CyA + ATP (N = 4)	CyA + V (N = 4)	Cya + ATP + V (N = 4)
State 3	170 ± 16.5	186 ± 23.0	183 ± 11.0	161 ± 2.6*†	141 ± 10.2*†	180 ± 15.7
State 4	46.0 ± 3.5	55.5 ± 6.4	55.2 ± 4.9	63 ± 3.1*†	55 ± 4.5	55 ± 2.6
Uncoupled	194 ± 13	197 ± 22	176 ± 13	174 ± 7	166 ± 9	186 ± 14
RCR	3.7 ± 0.2	3.4 ± 0.1	3.4 ± 0.3	2.6 ± 0.1*†	2.6 ± 0.2	3.3 ± 0.1
ADP/O	1.7 ± 0.1	1.7 ± 0.1	1.5 ± 0.1*	1.6 ± 0.1	1.6 ± 0.1	1.6 ± 0.2

Cortical mitochondria were isolated and placed in a closed reaction vessel fitted with a Clark O_2 electrode and containing an incubating medium of 120 mM KCl, 2 mM phosphate, 4 μM rotenone, 1 mM EGTA, and 5 mM K-succinate. State 3 respiration (μmoles O_2/gm min) was the O_2 consumption measured when 300 μmoles ADP was added and State 4 respiration (μmoles O_2/gm/min) was the basal O_2 consumption when all ADP had been converted to ATP. The respiratory control ratio (RCR = State 3/State 4) is an indicator of how tightly coupled the mitochondria are and assesses the integrity of the mitochondria preparation. The uncoupled respiratory rate (μmol O_2/gm/min) is the maximal O_2 consumption in the presence of an uncoupler of oxidative phosphorylation. ADP/O is the ratio of the known amount of ADP added to the amount of oxygen consumed during the burst of the State 3 respirations and expresses the efficiency of phosphorylation. CyA = cyclosporine; V = verapamil; ATP = ATP-$MgCl_2$; N = number of kidneys.

* $p < 0.05$ compared with *in vitro* control.

† $p < 0.05$ compared with CyA.

some fairly consistent changes seen overall in the proximal tubule cells, although these were heterogeneous among different nephrons in the same kidney.

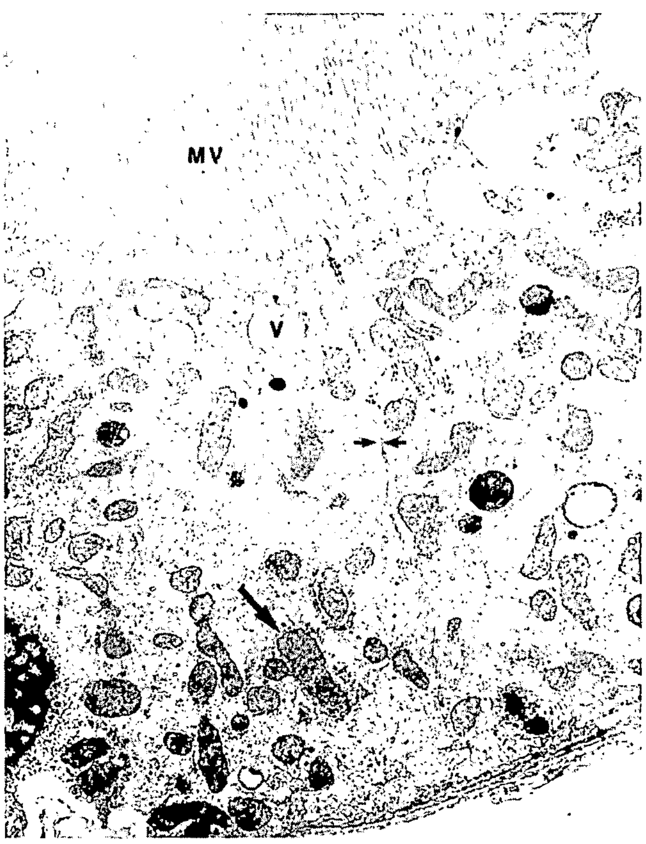

FIG. 1. Electron micrograph of proximal tubule segment of isolated rat kidney perfused for 100 minutes with 500 ng/mL cyclosporine. Note the appearance of vacuoles (V) and giant mitochondria (large arrow). MV = microvilli on apical portion of renal cell, small arrows showing cell junction. (Uranyl acetate-lead citrate, original magnification ×7000.)

The ultrastructure of a representative proximal tubule cell from a kidney treated with cyclosporine is shown in Figure 1. Although the presence of proximal tubule vacuoles (V) is also seen in the control group, the vacuoles appeared to be consistently increased in the CyA perfused kidneys and persisted despite treatment with ATP-$MgCl_2$ and verapamil. Occasional giant mitochondria (large arows) were also seen in the CyA-treated kidney.

Discussion

In our earlier studies,[1,2] 500 ng/mL of CyA in the perfusate led to a 90% reduction in GFR and a 67% fall in urine output with a lower but not statistically significant drop in renal perfusate flow. In addition, tubular reabsorption of protein, and to a lesser extent salt and water, was reduced acutely by CyA administration. In this study, mitochondrial function studies of kidneys after 100 minutes of CyA perfusion already showed a small but significant increase in mitochondrial calcium accumulation and statistically significant reduction in ADP/O, a measure of the efficiency of phosphorylation ratios. The increase in mitochondrial calcium occurred without a concomitant rise in tissue homogenate calcium levels. This suggests that the alterations are probably due to redistribution of intracellular calcium pools rather than a net influx of calcium from the extracellular compartment. A similar finding has been shown by Weinberg and coworkers in models of mercuric chloride and gentamicin nephrotoxicity.[11,12] Tissue and mitochondrial calcium accumulation did not occur until prolonged exposure to the nephrotoxins and just prior to development of cell necrosis. Studies with uranyl nitrate[13] have also suggested that an increase in mitochrondrial calcium may occur during the early phases of renal injury.

Evidence for cyclosporine-induced mitochondrial membrane damage is scant and conflicting. Humes and coworkers have reported a dose-dependent CyA inhibition of mitochondrial respiration supported by succinate in the S_3 segment of proximal tubule; however, no membrane permeability changes were noted.[14] Kirwan and collaborators showed that CyA had no effect on respiratory or oxidative phosphorylation in isolated rat renal cortical mitochondria or in mitochondria incubated from rats on chronic CyA administration.[15] Hay and coinvestigators have shown that CyA is associated with structural alteration in renal mitochondria at the molecular level, but this was predominantly in the medulla mitochondria rather than cortical mitochondria. They hypothesize that CyA interferes with mitochondrial biogenesis and replenishment rather than by direct inhibition of respiratory enzymes.[16] In our study, the mitochondria of CyA-treated kidneys were tightly coupled and effective in their normal function of oxidative phosphorylation, although the efficiency of phosphorylation (ADP/O ratios) is slightly lower. The finding of mitochondrial calcium accumulation and a decrease in ADP/O ratios after only 100 minutes of CyA perfusion may indicate an early subtle dysfunction that might manifest itself with longer periods of perfusion and CyA administration; however, further studies are needed in order to clarify these issues.

Histology of the CyA perfused kidneys showed increase vacuolization and occasional giant mitochondria in the proximal tubular cells compared to the control CyA vehicle perfused kidneys. These vacuoles varied in size and contained occasional dense bodies or myeloid bodies. The ultrastructure of the glomerulus and distal tubular cells, however, showed no abnormalities compared to the perfused control kidneys. Proximal tubule vacuolization has been reported by others[17,18] and is said to be consistent with clear lysosomes. The morphologic alterations induced by CyA seen in this study are consistent with those seen in whole animal models and with those in man,[19] although the latter is much more pronounced than in the experimental animal. The variability of the degree of morphologic findings has been viewed by some investigators as a result of cyclical toxicity,[18,19] but the lack of correlation between morphologic and functional parameters in other experimental models remains unclear. Nonetheless, it is important to bear in mind that CyA nephrotoxicity in man or animals is morphologically and functionally different from other forms of drug toxicity and that different pathogenic mechanisms probably underly the development of acute and chronic CyA toxicity.

Using the combination of verapamil pretreatment and ATP-$MgCl_2$ cotreatment with CyA almost completely reduced the nephrotoxic potential of this immunosuppressive agent.[1,2] GFR was restored to control values, renal perfusate flow and urine output were raised to supranormal levels, and tubular reabsorptive capacity was maintained at near control levels. The mechanism of the beneficial effect of this combination is not completely defined by the present study, but several interesting observations emerge. First, as previously reported,[1,2] the beneficial effects of ATP-$MgCl_2$ and the calcium channel blocker, verapamil, may be concentrated on different functional parameters with ATP-$MgCl_2$, improving tubular functions and tissue ATP levels while verapamil improved GFR, RPF, and urinary output primarily. Thus, the benefits of the combination therapy could be simply due to the sum of the effects of each drug. Secondly, the combination therapy resulted in ATP levels that were much higher than even the *in vivo* controls.[1,2] This supranormal ATP level might account for the marked improvement in function seen with verapamil and ATP-$MgCl_2$ administration with the increased intracellular ATP available for organelle utilization. Whether the high tissue ATP level might reflect a decreased but more efficient use of ATP or whether there is an actual increase in ATP production remains unknown.

Analysis of mitochondrial function of the various experimental subgroups indicates that while CyA administration resulted in no mitochondrial respiratory function abnormalities and only a slight accumulation of mitochondrial calcium, the addition of ATP-$MgCl_2$ resulted in an excessive accumulation of mitochondrial and tissue calcium leading to impaired respiratory mitochondrial function. Despite this impaired mitochondrial function, tissue ATP levels were still comparable, if not higher, than the untreated controls; this level of tissue ATP may be artificially lowered because of the impaired mitochondrial system. The results of this study indicate that the pretreatment with verapamil and cotreatment with the ATP-$MgCl_2$ corrected the mitochondrial dysfunction seen with ATP-$MgCl_2$ treatment alone and resulted in the supranormal tissue ATP levels seen with the combination therapy. High levels of calcium are known to produce a loss of mitochondrial function[20] and can lower the ATP synthetic activity.[21] Mitochondrial calcium transport takes precedence over oxidative phosphorylation.[22] The further loading of mitochondria with calcium leads to calcium phosphate precipitation and permeability changes in the membrane, which further inhibits oxidative phosphorylation. In addition, the permeability changes alter the electrochemical gradients responsible for ATP production. These calcium-induced mitochondrial permeability alterations can be mitigated by inhibiting the calcium influx. Zoccarato and colleagues have shown that Mg^{2+} and the adenine nucleotides can inhibit the uptake of externally added Ca^{2+} and phosphate.[23] Furthermore, intracellular calcium influx associated with ATP-$MgCl_2$ treatment has been demonstrated in the isolated hepatocyte model[24] and the resultant excess calcium accumulation by the mitochondria was postulated to impair ATP translocation from the mitochondria to the cytoplasm, thus lowering ATP stores.

The therapeutic implications of our *in vitro* studies become more important when one considers the most recent studies reporting that verapamil may potentiate CyA immunosuppressive properties. McMillen and coworkers have shown that verapamil would not only inhibit murine lymphocyte proliferation to lectin and alloantigen stimulation *in vitro* but, when given with CyA, can potentiate the inhibition of human lymphocyte proliferation.[25] Their studies taken together with the findings of this study suggest that the pretreatment with verapamil and the cotreatment of ATP-$MgCl_2$ with CyA would not only reduce the nephrotoxicity of CyA but, in addition, if verapamil enhances CyA immunosuppression, then a lower dose (and hence, less nephrotoxic potential) of CyA would be needed. Clinically this has important implications in providing transplant recipients with a less myelosuppressive and nephrotoxic agent.

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We make the Hemoclip® clip like it is because of the way nature made blood vessels.

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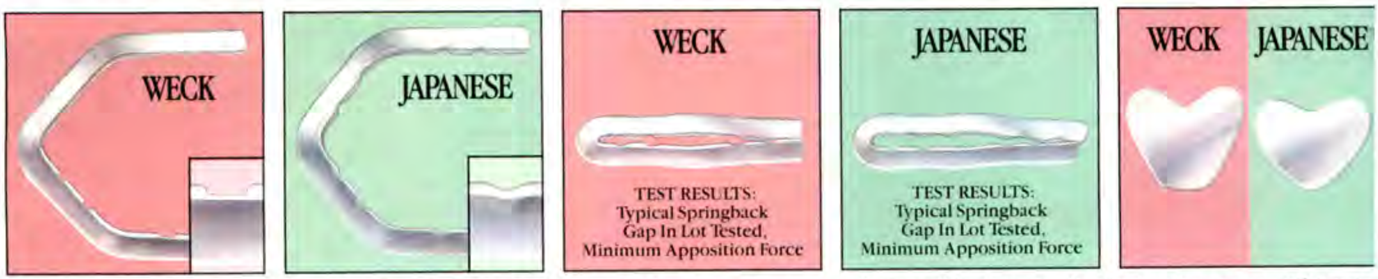
That sounds obvious, but it's not to everyone.

It's not easy to make ligating clips that are finely balanced between strength and malleability–two desirable ligating clip properties.

But in a quarter-century of manufacture, Weck has learned to do the job on this key implant device as no one else has.



The Hemoclip® ligating clip is coined with distinct rectangular transverse grooves, designed for longitudinal gripping power. Clip wire is processed metallurgially for malleability in closure. The Japanese imitation clips have shallow-drawn wire, and smaller, rounded transverse grooves. Deeper Hemoclip® wire shape aids retention in Weck appliers. (Typical closure illustrated from independent study.)

But now there's a problem you should be aware of. Some U.S.-based companies have begun distributing–not manufacturing–Japanese imitations of the Hemoclip® ligating clip. These clips are not the product of Weck manufacturing expertise and the technical performance of these clips is simply not the same as that of Hemoclip® ligating clips, an exclusive Weck product.

They may look the same, but they're not.

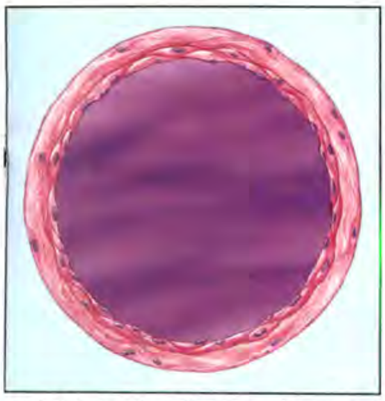
The recently-introduced Japanese clips look the same as Hemoclip® ligating clips to the naked eye. But a recently completed independent lab study of sample quantities of clips confirms Weck's own observation of substantial differences in closure properties between the Japanese clips and Weck clips.

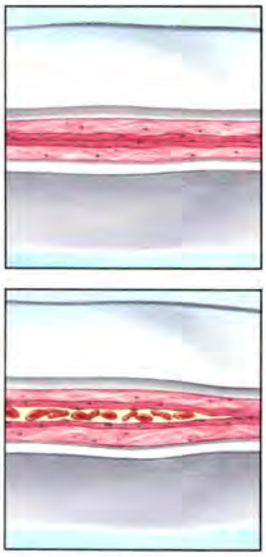
Vessel walls may be as thin as one-twelfth of vessel diameter.

Veins, in contrast to arteries, have very thin walls. When you consider that the vein tributaries ligated in surgery are sometimes one millimeter in diameter or smaller, with combined vessel walls as small as seven-thousandths of an inch (178 microns) according to animal studies on comparable vessels, you can appreciate the functional importance of differences in closure gap.

Arterial tributaries can be tiny, too, and although their walls are generally thicker than vein walls, arteria pressure is higher than venous pressure.

It seems prudent to employ ligating clips which offer the response and clip-closure performance Weck usage has established in your surgery





ABOVE. A vein tributary of 1mm can have a combined wall thickness of just seven-thousandths of an inch (178 microns), according to animal studies. RIGHT. A ligating clip that demonstrates greater springback than the clip you have regularly used for such vessels may be more likely to leave a closure gap larger than the vessel-wall thickness of a tiny vessel.

Weck's titanium clip vs. their titanium clip. A 23-27% difference.

Examine the chart for a visual representation of the difference in closure springback an independent research firm discovered between a set of Weck titanium medium-size clips and a set of Japanese titanium medium-size clips obtained directly from U.S. distributors of those clips. Both sets of clips were closed in Weck appliers through use of force-control devices.

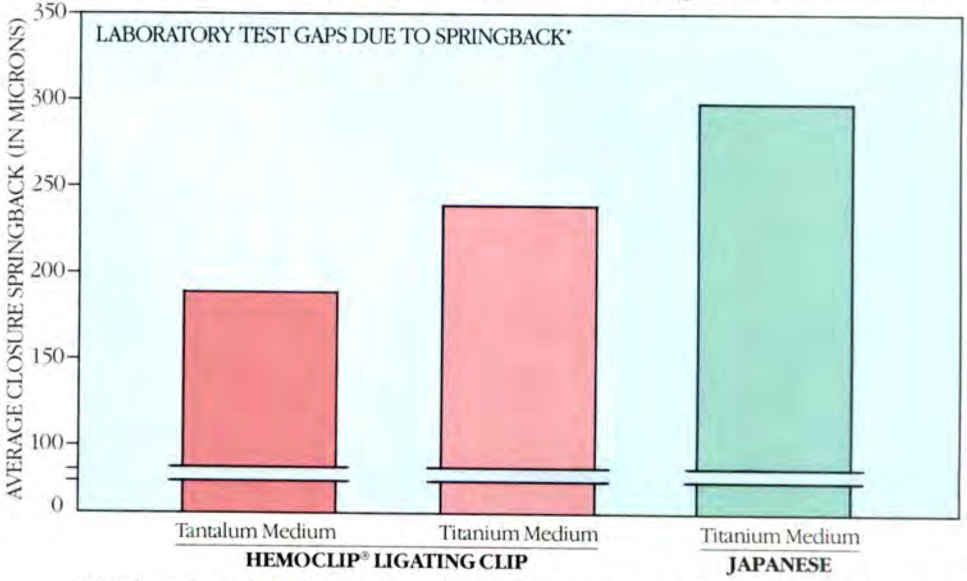
Closure of two sample sets of 25 Japanese titanium medium clips at forces adequate to achieve initial complete ouching along clip legs resulted in closures of about 12 thousandths of an inch (305 microns) for the Japanese clips, 23-27% larger than the Weck titanium clip closure gap.

Weck's tantalum clips vs. their titanium clips. A 56% springback difference.

The comparison of Japanese titanium with Weck tantalum clips is even more important.

The Japanese companies make only titanium clips, and so they have sold hard on the benefits of titanium.

Tantalum is a softer material known for excellent clip closure. And the study revealed 56% and 61% larger mean closure gaps after springback for two sets of Japanese titanium clips, a ringing endorsement of the closure advantages of the Weck tantalum clips tested.



An independent lab study on two sample sets of 25 Japanese imitation clips vs. Weck clips found that the Japanese medium-size clips, closed to initial complete touching of clip legs, evidenced mean closure gaps, due to springback, 23-27% larger than Weck medium-size titanium clips, and 56-61% larger than Hemoclip® tantalum clips from Weck. Other sizes produced similar results. (Closure gap in microns-one micron = one thousandth of one millimeter).

**Stronger closure forces would likely be employed during actual surgery cases.*

The comparison was similar for Weck stainless vs. Japanese titanium, with the stainless scoring substantially smaller gaps after springback.

Odds are, if you are using Weck clips you are accustomed to tantalum or stainless steel clip closure, because the vast majority of Weck accounts use these two metals.

And a new Weck-funded NMR major-university study indicates that magnetic deflection of tantalum clips is negligible, just as it is for titanium clips. So if your local competitive salesman distributing Japanese clips tries to convince you that titanium clips are exclusively acceptable for NMR magnetic deflection in preference to tantalum, we suggest you cite the new Weck-sponsored university study.

Look for the Weck name on the cartridge.

To visually and quickly confirm that you really are using Weck clips, look at the end of the clip cartridge. If you are using Weck clips, you should see there the Weck name molded into the plastic The Weck name is your assurance of genuine Hemoclip® clip processing experience and knowledge.

Perfection In A Surgeon's Hand.™ WECK®
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If you would like more detailed information on any of the points covered here, write Edward Weck Incorporated, P. O. Box 12600, Research Triangle Park, NC 27709. 1-800-334-8511. In NC 1-800-672-6583.

Improved Results from a Standardized Approach in Treating Patients with Necrotizing Fasciitis

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Necrotizing fasciitis has been associated with significant morbidity and mortality. Thirty-three patients were studied over a 3-year period. Predisposing factors included intravenous drug abuse (30%), diabetes (21%), and obesity (18%). Severe pain (94%) and abnormal temperature (88%) were present, whereas laboratory data and x-ray were nonspecific. Gram-positive organisms were most frequently recovered (B-hemolytic streptococcus 45%). Treatment consisted of antibiotics, surgical debridement, re-exploration 24 hours before surgery, nutritional support, and early soft tissue coverage as needed. Mean duration from admission to operation was 43 hours. The average number of operative debridements was three and the average length of hospitalization was 47 days. Patients operated on less than 12 hours from admission or greater than 48 hours had shorter hospital stays (36 and 38 days). The critical time period was 12–48 hours after admission; all deaths (2) and amputations (3) were in this group and the average hospital stay was 62 days ($p < 0.05$). The number of operations did not correlate to hospital stay. Despite antibiotics and aggressive debridement, significant morbidity exists if operation is delayed more than 12 hours. Methods of early detection such as local bedside diagnostic incision and fascial inspection may be needed in high risk patients to further reduce the morbidity and mortality.

NECROTIZING FASCIITIS (NF) is a well-defined, persistent, and pervasive disease in which the fascia is the primary site of infection. The disease involves extensive necrosis of the superficial and deep fascia with concomitant thrombosis of the cutaneous microcirculation (Fig. 1). Necrotizing fasciitis has been described in medical texts since 1871[1] and in the surgical literature since 1924.[2] Since these reports the mortality rate for patients with NF has ranged from 8.7%[3] to as high as 73%[4] and, in most cases, has equalled or exceeded the 20% mortality originally reported by Meleney[2] over 60 years ago.

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Recently a significant increase in the incidence of NF initiated a review of our experience and that of others. Predisposing clinical factors, etiologic incident, microbiological results, surgical treatment, and clinical outcome were analyzed. A significant number of patients have immunodeficiency complicating a relatively minor etiologic event. Early diagnosis and a regimen of vigorous resuscitation, nutritional support, broad spectrum antibiotics, and aggressive debridement with mandatory re-exploration are crucial in patient management. The results of this study correlate the timing of operative treatment with patient morbidity and mortality.

Materials and Methods

The medical records of 33 patients with NF treated during the period from September 1983 to April 1986 at New York University Hospital, Bellevue Hospital, and Manhattan Veterans Administration Hospital were reviewed. The data studied included age, sex, duration of hospitalization, associated disease states, etiologic factors, laboratory findings, location of primary infection, bacteriology, and treatment methods. Of the 33 patients studied, 27 had confirmation of the NF diagnosis by pathologic examination and six patients had a clinical diagnosis of NF primarily based on operative findings.

Surgical treatment was instituted as soon as the diagnosis of NF was considered. Therapeutic guidelines included institution of vigorous fluid resuscitation, arterial and venous monitoring, broad spectrum antibiotics, and aggressive surgical debridement of the involved fascia. Mandatory reexploration was performed within 24 hours. Repeat explorations and debridements were performed daily as needed until all the necrotic tissue was

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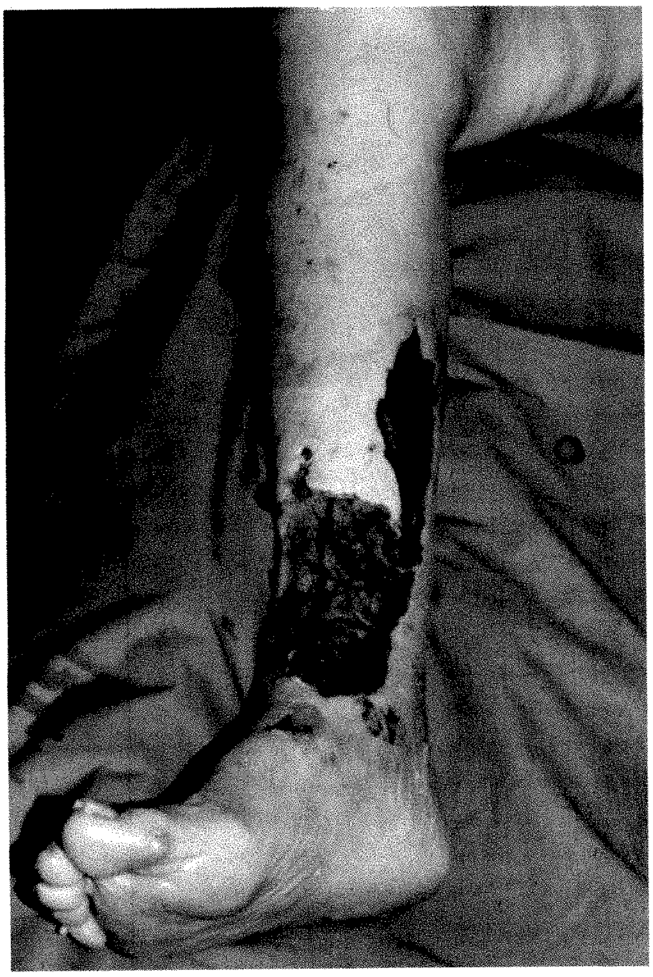

FIG. 1. Thrombosis of the cutaneous microcirculation.

erradicated. Medically unstable patients or patients in whom re-exploration revealed progression of infection in an extremity required amputation. Nutritional support was instituted with enteral or parenteral alimentation, supplying at least 3000 calories per day.

All results are expressed as the mean (±) standard deviation. Statistical analysis was performed using the F test with variance ratios.

TABLE 1. *Predisposing and Etiologic Factors in NF (33 Patients)*

Risk Factors	No. of Patients	Etiology	No. of Patients
IVDA	10 (30%)	IVDA	9 (27%)
Diabetes	7 (21%)	Skin infection	9 (27%)
Obesity	6 (18%)	Minor trauma	5 (15%)
PVD	5 (15%)	Perirectal infection	5 (15%)
Malnutrition	5 (15%)	Incarcerated hernia	2 (6%)
IVDA + diabetes	3 (9%)	Bites	2 (6%)
Paraplegia	1 (3%)	Postoperative	1 (3%)
Postoperative	1 (3%)		
None	3 (9%)		

Results

Risk Factors

There were 22 male and 11 female patients ranging in age from 25 to 78 years (mean ± SD = 46.2 ± 12.8 years). Ten of the 33 patients were intravenous drug abusers (IVDA) and seven were diabetic. Three patients were both diabetic and IVDA. Six patients were morbidly obese, five had clinical or laboratory evidence of malnutrition (serum albumin < 3.0 gm/dL), and five had peripheral vascular disease (PVD). Although three patients had no known predisposing factors, ten patients had more than one risk factor (30%) (Table 1).

Etiology

The most common events leading to NF in the 33 patients studied were minor skin infections (27%), intravenous drug injection (27%), minor trauma (15%), and perirectal abscesses (15%). Necrotizing fasciitis also resulted from complications of incarcerated herniae, animal and insect bites, and after surgery as a complication of an exploratory laparotomy for diffuse carcinomatosis (Table 1).

Signs and Symptoms

Thirty-one of the 33 patients (94%) presented to the hospital complaining of severe pain. One patient without pain was paraplegic with a perirectal infection source and the other was obtunded with organic brain syndrome. At the time of operative intervention, 24 patients (73%) treated with intravenous antibiotics for at least 1 day had progression of the infection. Twenty-five patients (76%) had developed cellulitis and skin changes (*i.e.*, blebs, ulceration, or frank skin necrosis). Twenty-seven patients (82%) had a temperature greater than 101 F, two patients had a temperature less than 97 F, and only four patients were normothermic. In six patients crepitus was present on physical examination (Table 2).

Site of Infection

Twenty-two of 33 patients (67%) had extremity lesions, 17 (52%) upper and five (15%) lower. In eight patients (24%) perineal infections extended to the buttocks and upper thighs. Necrotizing infections of the trunk were less common, occurring in three patients (9%).

Laboratory Findings

Abnormalities in red and white blood cell count, serum calcium levels, and acid-base balance were observed (Table 2). Anemia (hematocrit < 35%) (64%), hypocalcemia (Ca < 8.5 mg/dL) (33%), acidosis (arterial blood gas pH < 7.36 or serum bicarbonate < 20 mmol/L) (27%), and leukocytosis (>10.0 cells/mm^3) (88%) were the abnormalities most frequently found. One patient suffering from acquired immune deficiency syndrome (AIDS) was leukopenic (<3.0 cells/mm^3). Soft tissue radiography demonstrated gas in eight patients (24%) (Table 2).

Bacteriology

The average number of bacterial types isolated from each infection site was 1.95. Beta-hemolytic *Streptococcus* was the organism most frequently cultured (Table 3). *Escherichia coli,* alpha-hemolytic *Streptococcus,* and *Staphylococcus aureus* were also common. In patients with mixed infections a wide variety of gram-negative rods were present in operative cultures, while in monomicrobial infections *E. coli* was recovered. *Staphylococcus epidermis,* anaerobic diptheroids, microaerophilic Streptococcus, and Peptostreptococcus were also occasionally cultured. Two patients had no organisms recovered.

Morbidity and Mortality

Seven patients (21%) underwent surgery within 12 hours of admission (Group A) and ten (30%) patients after 48 hours (Group B) (Table 4). The mean hospital stay for these patients was 36 days (Group A) and 38 days (Group B), respectively. There were no deaths or amputations in these two groups. Sixteen patients (49%) were operated on between 12 and 48 hours (Group C), with a mean hospital stay of 62 days. The increase in hospital morbidity of Group C patients was statistically significant when compared with patients in Groups A and B. There were two deaths and three amputations in Group C patients. The number of operative procedures did not correlate with the patient group or hospital morbidity. The mean number of operative procedures for all patients was 3.24 ± 1.0. Two of the 33 patients died as a direct result of NF and a third patient died during the hospitalization from unrelated factors, resulting in a mortality rate of 6.1%.

Discussion

Necrotizing fasciitis is no longer an uncommon disease rarely reported in medical or surgical literature. Awareness of this potentially fatal infection and an increase in the number of patients with predisposing factors have contributed to the overall increase in incidence. In our series, 33 patients with NF were identified in 31 months. Patients with NF and other necrotizing soft tissue infections not involving the fascia are managed on a daily basis at our institution.

TABLE 2. *Clinical and Laboratory Date in NF (33 Patients)*

Clinical Signs and Symptoms	No. of Patients	Laboratory	No. of Patients
Severe pain	31 (94%)	Leukocytosis	29 (88%)
Temperature abnormalities		Anemia	21 (64%)
>101 F	27 (82%)	Hypocalcemia	11 (33%)
<97 F	2 (6%)	Acidosis	9 (27%)
Skin changes	25 (76%)	Gas (x-ray)	8 (24%)
Cellulitis—progressive	24 (73%)		
Crepitus	6 (18%)		

Earlier interest in this disease centered on developing anatomic or bacteriological classifications. Attempts were made to correlate the site of infection and the presence or absence of skin involvement with clinical factors. The microbiology of infection has also been studied extensively. No clinical differences or improvement in patient survival were evident in studies of individual bacteria. In general, however, polymicrobial infections have longer clinical incubation periods than monomicrobial infections, making the former more difficult to detect at an early stage.

The mean mortality rate reported in previous studies of NF between 1924 and 1986 is 32.2 ± 18.8% and ranges from 8.7% to 73.0%.[2–4,6–14] The wide range and high mean mortality rate reported in these studies reflect differences in definitions and diagnostic criteria for NF, prevalence of risk factors and etiology among the patient populations studied, and variations in the effectiveness of the treatment methods.

The mortality rates have been reported to be especially high in the presence of old age, peripheral vascular disease, and diabetes. The common factor in our patients is an underlying immune defect due to one or

TABLE 3. *Microbiology in Patients with NF*

Bacteria	No. of Patients
Gram-positive	
B-hemolytic Streptococcus	15 (45.4%)
Staphylococcus aureus	8 (24.2%)
A-hemolytic Streptococcus	8 (24.2%)
Staphylococcus epidermis	6 (18.2%)
Gram-negative	
Escherichia coli	8 (24.2%)
Enterococcus	4 (12.1%)
Klebsiella pneumoniae	4 (12.1%)
Proteus mirabilis	4 (12.1%)
Pseudomonas aeruginosa	3 (9.1%)
Enterobacter sp.	1 (3.0%)
Anaerobes	
Diptheroids	4 (12.1%)
Microaerophilic	1 (3.0%)
Peptostreptococcus	1 (3.0%)
No organisms identified	2 (6.1%)

TABLE 4. *Analysis of the Hospital Morbidity of NF*

Group	No. of Patients	No. of Debridements	Average Stay (Days)
A (<12 hrs)	7	3.0 ± 1.1	36
B (>48 hrs)	10	3.3 ± 1.0	38
C (12–48 hrs)	16	3.2 ± 1.2	62
Total (43 hrs)	33	3.24 ± 1.1	47.1

more diseases (91%); only three patients who were otherwise healthy developed NF. The most common predisposing conditions included intravenous (IV) drug abuse, diabetes, or both (61%) (Table 1). A significant percentage of patients (48%) had peripheral vascular disease, obesity, or malnutrition; 30% patients had more than one risk factor. Rea et al.[7] noted a 67% mortality in patients with NF who were older than 50 years. In our series one patient over 50 years of age died for a mortality of 7.1% in this age group. Many of our patients (30%) were IV drug abusers, the group reported to have a lower mortality from NF than diabetics. Melluzzo et al.[16] reported no deaths in three cases of NF related to IV drug abuse and Schecter et al.[15] reported only one death among 21 NF patients who were IV drug abusers.[15] Mortality rates of up to 80% have been reported for NF in diabetics.[4] None of the patients suffering from diabetes or IV drug abuse died in this study.

Etiologic incidents in our patients were IV drug injection, skin infections, minor trauma, or perirectal abscess (Table 1). In an earlier report by Rea et al.[7] on a series of 44 patients with NF, minor trauma was the initiating event in 80% of the cases and the reported mortality was 30%. In contrast, in the current series 54% of the patients developed NF directly from IV drug abuse or minor skin infections, and 30% of the patients developed NF from minor trauma or perirectal infections. The overall mortality rate was 6.1%. Disparities in etiology and mortality may reflect differences in patient populations studied. However, early detection and effective therapy have been associated with lower mortality.[5]

The most common presenting complaint was severe pain in the affected region, often of a severity disproportionate to the local physical findings (Table 2). This symptom was present in all patients except for two with alteration in pain response due to neurologic dysfunction. The pain was frequently associated with signs of systemic toxicity, including hypo- or hyperthermia, abnormal white blood cell count, and acidosis. Classically, NF has been associated with skin changes in less than 50% of patients. However, factors such as etiology, delay in presentation, and the type of bacteria account for variations in this aspect of clinical presentation. In our series local physical findings most often included extension to the skin with changes such as blebs, ulcers, o necrosis superimposed on pre-existing cellulitis. A striking finding was the progression of cellulitis during hospitalization despite the administration of appropriate broad spectrum antibiotics. This skin change was evidence of continued underlying tissue necrosis. Crepitus was identified in only 18% of patients, usually as a late clinical sign.

Previous reports have suggested that patients with NF of the extremities have an improved survival compared to those with involvement of other areas.[4,12,15] In this study there were 22 extremity infections with one death (4.5% mortality rate), eight perineal infections with one death (12.4% mortality rate), and three trunk infections with no deaths.

At least one gram-positive organism was cultured in 79% of patients. These included beta-hemolytic Streptococcus, *Staphylococcus aureus* and *epidermidis,* and alpha-hemolytic Streptococcus (Table 3). Gram-negative rods were recovered in 73% of patients. Two patients had pure gram-negative organism infections and eight had pure gram-positive infections. Fourteen patients had mixed gram-positive (Staphylococcus or Streptococcus) and gram-negative organisms, and two patients had sterile cultures. In six patients, anaerobic or microaerophilic organisms were found in combination with gram-positive and gram-negative organisms. NF is usually a polymicrobial disease caused by diverse organisms, usually two or more. These findings confirm the observation that NF is a clinical pathologic process affecting an organ system, the fascia, which is independent of the specific bacteria present.[8] The finding of Streptococcus, gram-negative aerobes, and anaerobes supports the use of a combination of high-dose penicillin, an aminoglycoside, and clindamycin or metronidazole as the empiric agents of choice in patients with NF.

A standardized treatment was evaluated in this series of patients. All patients were treated by aggressive resuscitation, surgical debridement with mandatory re-exploration at 24 hours, and as clinically required, IV antibiotics, nutritional support, and early soft tissue coverage. All patients in this series had a diagnosis of NF that was confirmed by pathologic studies or documented clinically by the presence of liquefaction necrosis of the fasica, which allowed the surgeon to pass a blunt instrument or hand freely along the normally adherent tissue planes. The pathologic process seems based on vascular ischemia to the end vessels of the fascia, perhaps due to effects of exotoxin release. The fascia responds as a diseased organ system, resulting in initial local impairment and then systemic septic effects.

Our data support a policy of early fascial exploration for all patients in high risk groups presenting with severe pain, particularly if accompanied by cellulitis, local skin changes, or crepitus. Early fascial exploration is also indicated for all patients in whom cellulitis progresses and severe symptomatic toxicity develops despite administration of appropriate antibiotics.

Variability in the rate of development of NF was originally described by Wilson in 1942.[3] He noted that the infection may affect an entire extremity within 24 hours or slowly progress over several weeks. In other patients the disease is dormant and then spreads rapidly without any readily apparent reason. Our study identified three clinical groups of patients that may represent these differences. The patients with rapidly progressive disease who were debrided less than 12 hours after admission (Group A) had the same hospital morbidity as the patients with infection that spread slowly and required operation after 48 hours (Group B). However, patients with rapidly progressive infection in whom debridement was delayed for 12–48 hours (Group B) remained hospitalized significantly longer (Table 4). The most serious sequelae of NF (death and amputation) were observed in patients operated on more than 12 hours after admission. This confirms the study of Kaiser and coworkers,[5] which indicated that the length of delay between recognition of a surgical infection and initiation of surgical therapy had a significant positive correlation with mortality.

The factors that cause NF to be aggressive or even lethal within 24 hours in some patients and remain relatively unaggressive in others remain unidentified. The virulent phase of this disease must be diagnosed quickly and accurately. Exploration and fascial examination of suspicious areas can easily be performed under local anesthesia at the bedside by incision and inspection of the fascia noting the color, odor, presence of necrosis, and status of fascial planes. Liquefaction necrosis, grey nonviable fascia, or separation of the fascia from the subcutaneous tissue or muscle indicate the need for operative debridement. The results of this study suggest that there is an increased incidence of the disease. The common clinical presentation involves an IVDA or diabetic with a minor skin infection of an extremity. The significant findings are severe pain, fever, and progressive cellulitis, accompanied by anemia and leukocytosis. The diagnosis is based on frequent physical examination and confirmed by inspection of the fascia either locally or in surgery. Definite treatment includes a unified plan consisting of vigorous preoperative resuscitation, broad spectrum antibiotics (including penicillin), aggressive surgical debridement with mandatory re-exploration at 24 hours and thereafter as needed, parenteral or enteral nutritional support, and early soft tissue coverage. With the above approach the overall hospital morbidity was 47 days and the mortality rate was 6.1%.

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PTFE Grafts for Hemodialysis Access

Techniques for Insertion and Management of Complications

SESHADRI RAJU, M.D.

In a series of 602 procedures, over 90% of primary forearm insertions of PTFE grafts between the radial artery and a cubital vein were possible. Thrombosis of the graft, which was invariably due to venous outflow obstruction, was the most common complication encountered. Revision of the venous anastomosis was not necessary in about one-third of the thrombosed grafts if a size 3 coronary dilator could be passed and the augmentation test was satisfactory. For revisions, creation of a new venous anastomosis using a jump graft was preferred over patch angioplasty or venous endarterectomy. Crossing the elbow for this purpose did not adversely affect graft patency. The incidence of aneurysm formation and infection was 16% and 35%, respectively. Infections involving the graft were managed by drainage, antibiotics, and bypass of the infected portion. Immediate bypass and delayed bypass were equally effective. About one-half of the infected grafts were salvaged by these techniques. The most common organism was *Staphylococcus aureus*. With a combination of the techniques outlined above, the service life of individual PTFE grafts can be extended. Two-year access patency in this series was 77%.

WITH THE INCREASING NUMBER of patients sustained on chronic hemodialysis, access related surgery forms a significant proportion of vascular surgical practice today. A cursory review of current procedures reveals a considerable variety in techniques of insertion and in the management of complications. For example, some centers prefer the upper arm straight graft[1,2] while some others advocate the forearm loop.[3,4] Considerable differences exist in the choice of artery or vein and the location for access insertion. In this report, we present our experience with over 600 dialysis access grafts, emphasizing insertion technique and management of complications.

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Materials and Methods

A total of 602 PTFE hemodialysis access grafts wer inserted in 532 patients at the University of Mississipp Medical Center during the period 1976–1986. Othe types of access fistulae, such as Cimino AV fistula Scribner shunt, etc., were excluded from this review. substantial number of patients were lost to follow-u because of transfer to other chronic dialysis facilities an other reasons (Table 1). Adequate follow-up data wer available on 312 grafts.

Insertion Technique

A straight graft in the forearm of the nondominan hand was preferred. Local anesthesia (1% Xylocaine infiltration) was used, except in the occasional instanc in which a general anesthetic was required for poor pai tolerance, uncooperativeness, extreme apprehension, o other reasons. Patients subjected to local anesthetic wer not kept NPO as a general rule, thus ensuring uninterrupted continuation of scheduled medications (*e.g.*, antihypertensives) and allowing flexible scheduling without extended fasting. Patients were premedicated wit oral Valium® given on call. A second generation cephalosporine was administered intramuscularly at the sam time.

The radial artery was exposed near the wrist with 1-inch longitudinal incision. The antecubital vein exposed through a transverse incision was the preferre outflow. When this vein was unavailable due to inadequate size or thombosis from previous venipuncture, th cephalic or basilic vein was chosen. Tunneling an placement of the graft between the two incisions wa

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TABLE 1. *PTFE Grafts for Dialysis Access*

602 grafts in 532 patients
↓
Transfer, transplant, peritoneal dialysis, death, or inadequate follow-up
↓
312 grafts with 1–10-year follow-up

carried out before heparin (5000 U) was given. The technique of tunneling was considered important. The tunneling instrument should be somewhat smaller than the 6-mm size access graft. This ensures tamponade of the tunnel by the distended graft, which helps to secure hemostasis and prevent tunnel hematoma and subsequent infection. The long "disposable" metal trocar that is often supplied with chest tubes was particularly suitable for this purpose. A hole drilled through the end allows easy fixation of the graft to this tunneling device. The metal trocar is easily bent into any shape required for tunneling. The graft should be placed as subcutaneously as possible (Fig. 1). Counter pressure applied against the tip of the tunneling device with a sponge helps to achieve this placement. Deeper placement of the graft results in difficult access puncture, frequently leading to multiple holes, tears, and perigraft hematoma resulting in compartmental syndromes, or infection. The tunnel should be deeper near the incisions (Fig. 1A, offset) to provide for thick flaps at those points to ensure prompt primary healing. Beveled anastomoses are made to the artery and vein with continuous 6-0 Prolene using loop magnification. Heparin may be left unreversed if hemostasis is satisfactory after completion of the anastomoses.

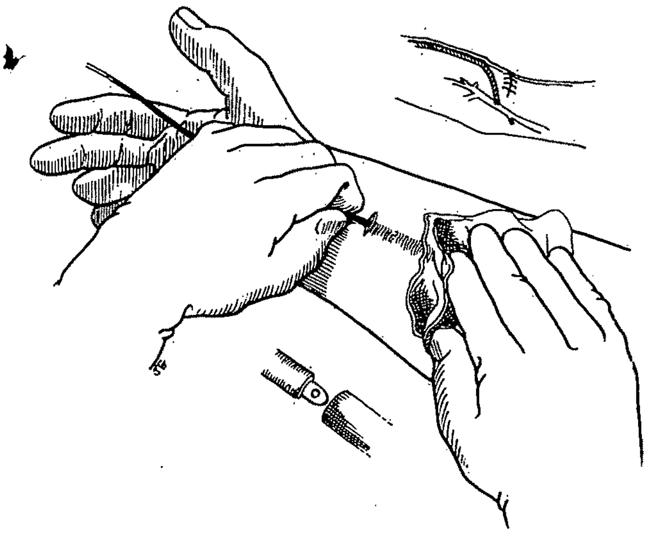

FIG. 1A. Tunneling techniques. Counter pressure against the instrument assures a superficially located tunnel. The tunneling instrument should be somewhat smaller in size than the graft diameter to ensure tamponade of the tunnel by the distended graft (offset below).

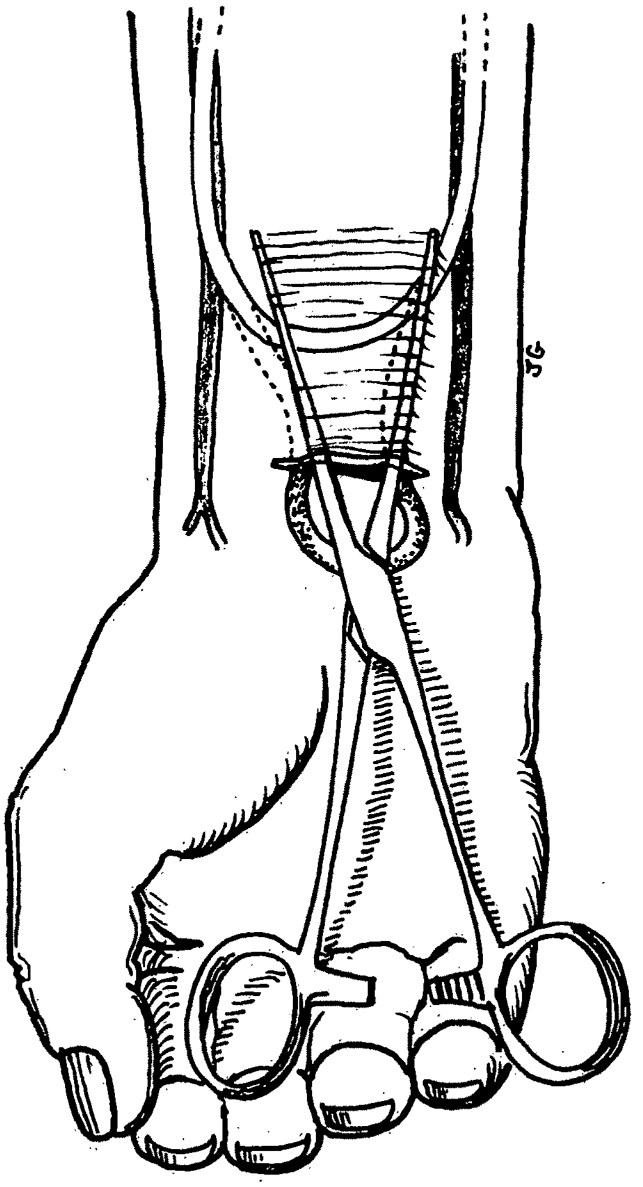

FIG. 1B. In looped grafts, counter incision for tunneling should not be located over the loop to avoid erosion by the graft. The maneuver depicted allows dislocation of the loop away from the incision.

After the procedure, the pulsatility of the graft should be monitored with and without clamp occlusion of the outflow end of the graft. A palpable increase in pulsatility with this maneuver confirms satisfactory outflow. In our experience, this maneuver has been more reliable than palpating "thrill" for this purpose. Since the most common cause of early graft thrombosis is inadequate outflow, this step is particularly important. Orally administered antibiotic with antistaphylococcal activity, usually cephalosporine or other, is continued for 3 to 5 days after surgery. The patient is instructed to avoid

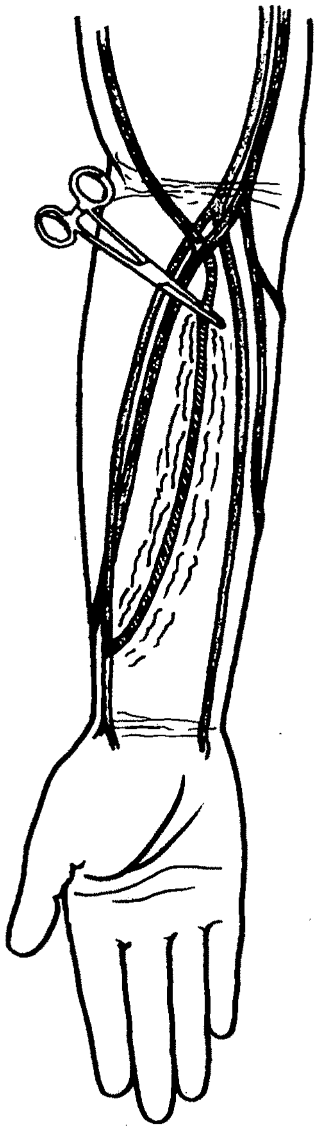

FIG. 2. Augmentation test to ensure adequate venous outflow to the graft. A palpable increase in pulsatility on occlusion of the outflow end confirms satisfactory outflow.

sleeping with the elbow bent acutely and to keep the arm elevated on a pillow for a few days after surgery.

Management of Complications

Thrombosis of the graft. A thrombosed access graft should be examined for palpable pulsations near the arterial end. These are invariably present, suggesting a problem at the venous end. Absence of pulsations at the arterial end of the graft may indicate poor inflow or propagation of thrombus into the arterial tree. Thrombosed grafts should be approached through the old antecubital incision used for construction of the venous anastomosis. A newer incision, creating a bridge of skin between two incisions with tenuous blood supply, is considered unnecessary. Circumferential control of the graft is likewise unnecessary and may lead to injuring the deep surface of the graft while attempting to pass an instrument around it. An incision is made over the "cobra head" in the prosthesis and the venous side thrombectomized with a Fogarty catheter. Heparin (5000 U) is immediately instilled into the open vein *via* a catheter. A Fogarty catheter (number 3 or 4) should be used next to declot the graft from the arterial end. Retrieval of the bullet-shaped clot from the arterial end with establishment of satisfactory inflow denotes a successful effort. A separate incision over the arterial end of the graft may occasionally be necessary to establish complete and satisfactory thrombectomy.

In approximately one-third of cases, the revision of the venous end is unnecessary as the venous anastomosis easily admits a 3-mm or larger coronary dilator. A positive augmentation test for pulsatility as previously described denotes satisfactory outflow (Fig. 2). Absence of satisfactory augmentation indicates the need for revision of the venous end. Revision may be carried out by a jump graft with a new venous anastomosis to an adjoining vein (basilic or cephalic) or to the same vein in a more cephalad location. The jump graft can cross the elbow crease if necessary to achieve this purpose. Venous endarterectomy and patch venoplasty are less preferred alternative procedures for revising the venous anastomosis. Venous endarterectomy is carried out by scraping the hyperplastic new intima at the venous orifice with a #5 blade that is carefully swirled circumferentially through the anastomosis (Fig. 3). Forceful dilation of venous stenoses with coronary dilators is unsatisfactory and often leads to injury and rupture of the venous segment.

Revision of the arterial end. Stenosis of the arterial anastomosis can be enlarged satisfactorily by incising the stoma with a Pott's micro scissors, introduced through an incision in the access graft placed directly over the anastomosis (Fig. 4). The enlarged stoma should be secured by a few sutures of fine Prolene to prevent extravasation and false aneurysm formation. However, this is usually not a problem because the graft is generally adherent to the artery for some distance beyond the anastomosis. Arterial control for this procedure is preferably obtained by a tourniquet (see below), thus avoiding tedious circumferential dissection around the arterial anastomosis for vascular control.

False aneurysm. Tourniquet control with systemic heparinization provides satisfactory vascular control and minimizes the extent of dissection around the false aneurysm. With tourniquet control, the aneurysm is boldly incised and the clot evacuated. The destroyed access graft is trimmed until a healthy graft is encountered. The missing segment is replaced by introducing a new piece of PTFE graft within the bed of the false aneurysm and anastomosis to the ends of the old graft for continuity. More extensive destruction of the PTFE graft by extensive aneurysm formation from repeated needle punctures is more appropriately treated by defunctionalizing the entire segment and bypassing the damaged length with a fresh graft routed through a separate adjoining tunnel and anastomosed to the undamaged ends of the old graft. At least 3–5 cm of the old graft should be preserved at each end for dialysis puncture until the fresh graft matures. Stenotic lesions in the access graft from intimal build-up or partial destruction may be similarly treated by segmental bypass.

Infection. Extensive infection of the graft with cellulitis and involvement of the suture lines will usually require complete excision of the graft and drainage for satisfactory control of the infection and sepsis. More limited infections may be successfully managed by incision and drainage with adequate antibiotic coverage. Superficial infections and, occasionally, a deep infection of the graft may heal with this approach. More frequently, the infected segment of the graft must be excised and bypassed for salvage of the access device. The bypass may be done immediately prior to the incision and drainage, or as a staged procedure a few days later when the inflammatory reaction has subsided following incision and drainage (Fig. 5). Occasionally we have succeeded in salvaging a prosthesis involved with a very localized chronic infection, presenting as a chronic sinus, without a bypass. The sinus and the infected tissue are completely excised; the graft itself is scraped clean of tissue and covered by adjoining healthy tissue by primary closure. Systemic antibiotics are necessary for successful salvage.

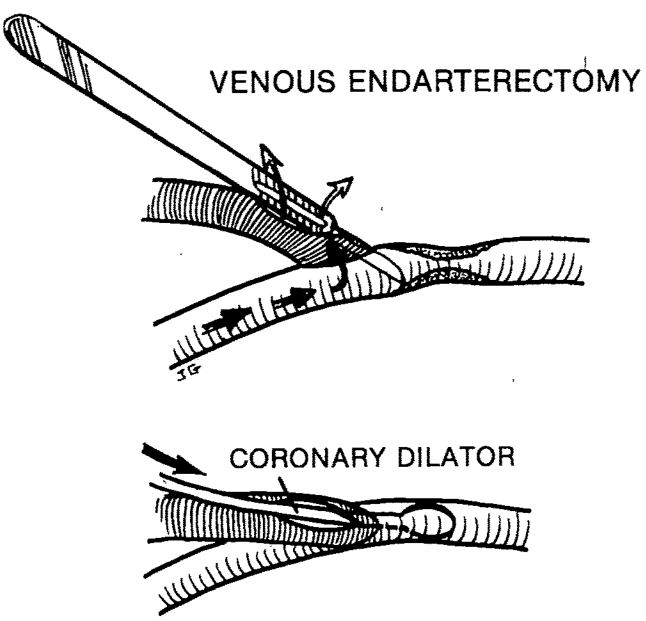

FIG. 3. Technique of venous endarterectomy. The coronary "dilator" should be used for sizing and minimal dilatation only. Ambitious dilatation usually results in false passage. Note "backbleeding" from distal vein.

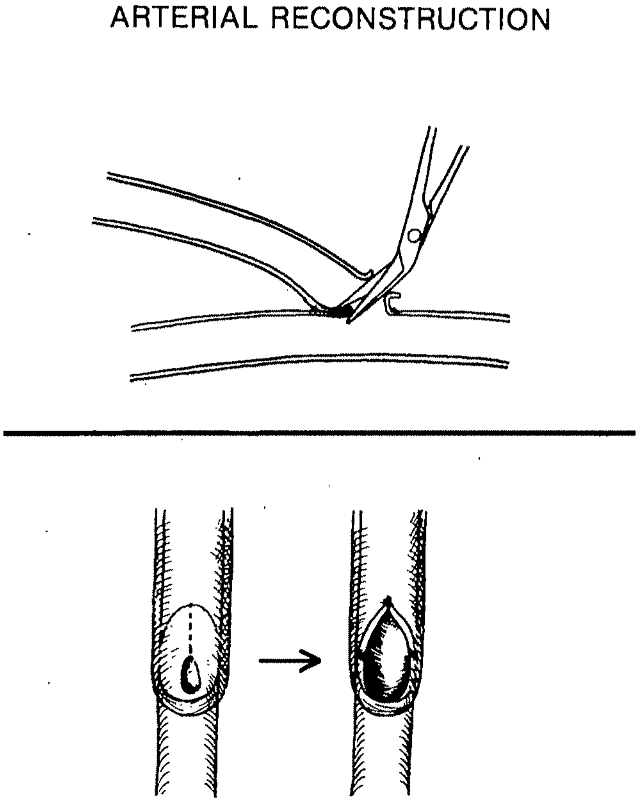

FIG. 4. Technique of arterial anastomotic revision. Because the graft is adherent to the artery for some distance, the common septum may be divided without fear of extravasation. A few sutures placed from inside ensure integrity of the stoma.

Results

Among the 602 forearm grafts inserted, only 28 loop grafts used the brachial artery. In all others a straight graft originating from the radial artery was used. Of the 28 loop grafts, the brachial artery was electively used in 15. In 13 others the radial artery was initially examined and found to be unsuitable to carry inflow into the access. Only then was the brachial artery chosen for access inflow. Among the 312 grafts with adquate follow-up, the straight graft was converted into a loop with inflow

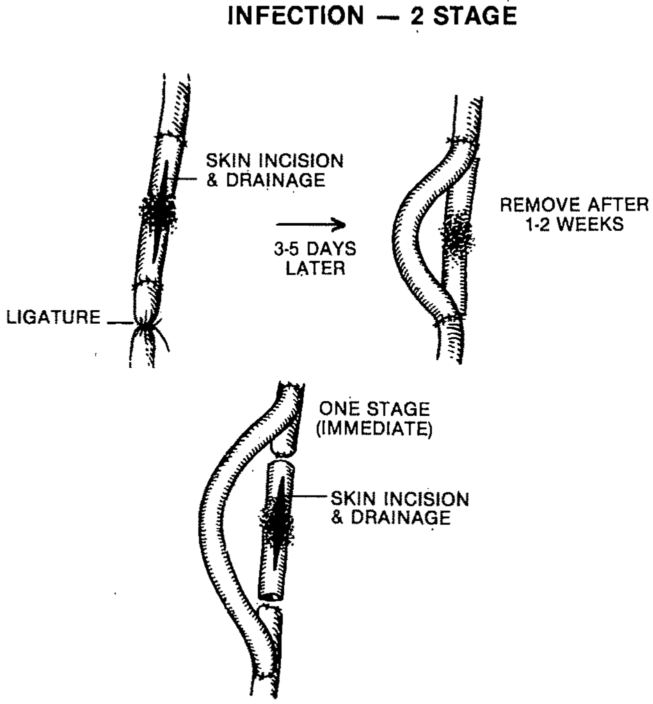

FIG. 5. Infections can be treated in two stages (top) with incision and drainage followed by a secondary bypass, or in one stage with a primary bypass (bottom).

from the brachial artery in a total of 17 grafts. Conversion was dictated by infection (5 grafts), inadequate radial artery inflow (8 grafts), or other technical reasons (2 grafts). Among the 312 grafts followed for a year or more, no further complications presented in 117. Complications were encountered in 195 grafts (64%). The mean interval between insertion and onset of first complication was 330 days for these 195 grafts. Of these 195 grafts, 124 suffered a recurrent complication, with a mean time interval of 182 days. A third complication was encountered in 62 grafts with a mean time interval of 178 days (*i.e.*, complication-free interval was stable for grafts suffering from recurrent complications).

The variety and incidence of complications are listed in Table 2. There were 372 primary and recurrent complication events in these 312 PTFE grafts. Thrombosis was the most frequently encountered complication, occurring in two thirds of the access grafts. Approximately one third of the complications were infection-related. Fifty false aneurysms were encountered in this series, usually due to repeated needle puncture at the same graft site. There were six instances of steal and three of gangrene in this series. Two of the three patients with gangrene were diabetic and carrying loop grafts from the brachial artery. There were no instances of access-induced cardiac failure in this group.

TABLE 2. *312 PTFE Grafts for Dialysis: Complications (1–10-Year Follow-up)*

	N	Per Cent of Incidence
Thrombosis	203	(64)
Infection	110	(35)
False aneurysm (repeated needle puncture)	50	(16)
Steal/gangrene	6/3	(3)
Heart failure	0	(0)

TABLE 3. *Access Thrombosis*

203 Initial Episodes		282 Total Episodes	
Early (<2 wks)	8%*	"Simple"	37%
Late	76%†	2° to stenosis	63%
Access Stenosis			
Venous	67%	2/3 of stenoses at venous end	
Arterial	15%		
Graft	18%		

* Calculated for 602 insertions.
† Calculated for 312 grafts with adequate follow-up.

Access Thrombosis. There were 203 initial episodes of graft thrombosis and 282 total episodes including recurrent thrombosis. Twenty-four per cent of initial episodes (49 in 602 insertions for 8% incidence) were early, occurring within 2 weeks of graft insertion, while 76% occurred later. Over one-third (37%) of all thrombotic episodes were classified as simple (*i.e.*, no technical basis such as stenosis or poor inflow could account for the thrombosis). In the remaining two-thirds, a structural basis required surgical revision of the graft. Two-thirds of the revisions were needed at the venous end (Table 3). Arterial revision was required in 15% and replacement of a segment of stenosed or destroyed graft was necessary in 15%. In approximately one-third of the episodes requiring graft and/or arterial anastomotic revision, a concomitant venous revision was also necessary (Table 4). Jump graft with the new venous anastomosis was the preferred method of revision. Venous endarterectomy (Fig. 3) was resorted to in 13% of venous revisions. Patch venoplasty was used in 8%, often in association with venous endarterectomy (Table 4). Crossing the elbow crease for segmental revision did not adversely affect graft patency or recurrent thrombosis.

Graft infection. There were 110 episodes of infection in these 312 grafts. Staphylococcus was the most common infection (54%). Other organisms were encountered in 10%. In a surprisingly large number (36%) with clinical infection, there was no growth on bacteriological culture. This is possibly related to antibiotic coverage prior to culture or the presence of a responsible anaerobic organism, as anaerobic culture was not routinely done in these instances. Ninety grafts required surgical intervention for control of infection. Six of these 90 were nonfunctional old grafts and were simply excised. The infection was serious enough to warrant excision and abandonment of 24 functioning grafts. Simple incision, drainage, and systemic antibiotics was the mode of treatment in nine grafts. Six of these were subsequently salvaged with elimination of infection. The three grafts that did not respond to this treatment regimen were abandoned. Localized infection was excised and the graft covered over by fresh tissue in seven grafts. This maneuver eliminated infection in three, while the remaining four required subsequent excision of the graft and abandonment.

A local bypass around the area of infection was performed in 44 grafts. Thirty-nine (90%) had successful salvage of the graft with this maneuver. In 28 instances, the bypass was classified as primary (*i.e.,* the bypass was performed at the same sitting as the incision and drainage). In 16 others, the bypass was performed a few days after initial incision and drainage of the abscess with ligation of the graft to stall flow through the infected area. There was no difference in the salvage rate between primary and secondary bypass methods (Table 5).

The modified patency rate of the 312 grafts studied was 93% at 1 year and 77% at 2 years. The term "modified patency" denotes inclusion in survival statistics of those grafts salvaged by appropriate surgical intervention for management of the aforementioned complications.

Discussion

Certain principles of technique in dialysis access surgery using PTFE grafts merit emphasis. When possible, the graft should be placed in an accessible location (forearm) of the nondominant limb. The graft should be placed as superficially as feasible beneath the skin so that access puncture is easy, thus helping to minimize injury to the graft from multiple punctures, tangential punctures, etc. In our experience, the radial artery is preferred for the takeoff of the PTFE graft. Because of the natural size limitations of inflow, cardiac failure is virtually absent when this vessel is used. Since thrombotic and infectious complications are quite common in this group of patients, the choice of radial artery for initial insertion allows the option of moving up the arm to other arterial locations if the primary graft should be abandoned from complications. With infectious complications involving the suture line, the potential threat to limb or life is also much less when the radial artery is used rather than brachial or more proximal arterial points of takeoff. Most of the published reports[3,5] have used upper arm or loop grafts for PTFE dialysis grafts. The incidence of thrombotic and infectious complications reported in these more proximally located grafts, with a larger inflow artery, is in many respects quite similar to our experience with straight grafts reported herein.

TABLE 4. *Dialysis Access: Thrombectomy/Revision (282 Procedures)*

	Per Cent
Simple thrombectomy (103)	37
Thrombectomy with revision (179) *(approximately 2/3 require revision)*	63
Segmental replacement (156/179)	87
Venous endarterectomy (23/179) (8% with patch venoplasty)	13

The most common complication in our and other series[6,7] continues to be thrombosis of the graft. In about one-third of these complications, the thrombosis is cryptogenic (*i.e.,* no structural basis for thombosis could be found). In the other two-thirds, however, a stenosis was usually found at the venous end. For this reason, the venous anastomosis must be constructed meticulously with assurance of an excellent runoff at the time of primary insertion. This could help to reduce the incidence of early thrombosis of the grafts even though late thrombosis from intimal hyperplasia appears insensitive to good insertion technique. In our experience, the augmentation maneuver described in Figure 2 has been more useful to gauge adequate outflow than is monitoring for a thrill at the venous end. It is important to make the venous anastomosis to one of the named veins in the antecubital region. Unnamed subcutaneous veins, however large, have been disappointing in providing lasting runoff. The reason for this may be kinking of subcutane-

TABLE 5. *Salvage* Procedures for Access Infection*

	N	Success	Failure
Bypass (total)	44	39	5
Primary	28	26	2
Secondary	16	13	3
Incision and drainage antibiotics	9	6	3
Excision of sinus, primary closure	7	3	4
Total	60	48	12

* Thirty grafts were abandoned for extensive infection and required excision.

ous veins with elbow flexion, which does not appear to be a problem with the named veins situated beneath the fascia. Systemic heparinization is routinely used to prevent intraoperative vascular thrombosis.

Despite ensuring adequate runoff, some PTFE grafts repeatedly thrombose in the early period after insertion. The precise cause for this is not clear. Flexion of the elbow, creating kinking of the graft at the venous outflow, dehydration and low perfusion state, prolonged compression of the relatively immature graft for hemostasis at the needle puncture site, or clotting of the dialysis lines and apparatus are possible explanations. Appropriate measures, including an arm pad to keep the upper limb extended, hydration, maintenance of adequate perfusion pressure, and careful technique during dialysis, should be exercised. Despite all these precautions, every dialysis center has seen the occasional patient in whom the PTFE graft must be abandoned because of recurrent unremittent thrombosis in favor of some other dialysis technique.

Few PTFE dialysis grafts escape thrombosis at some point during their dialysis life. The problem can be localized to the venous end when arterial pulsations are present at the arterial end of the graft. When these are absent, an inflow problem, along or combined with an outflow stenosis, should be expected. In any event, thrombectomy of the graft should be approached through the old skin incision used for the venous anastomosis. A separate skin incision some distance away creates a skin bridge with compromised blood supply and moves away from the point of anastomosis at which the stenotic problem usually resides. If satisfactory declotting is achieved and the venous anastomosis admits a 3-mm or larger coronary dilator, anastomotic revision is usually unnecessary.

While venous endarterectomy and vein patch angioplasty can be used to correct discrete stenosis at the venous takeoff, we have come to rely increasingly on a jump graft to bypass the stenosed area altogether. The jump graft can be anastomosed to the same or other adjoining vein in a virgin area. This is usually accomplished through the same skin incision, especially when the anastomosis can switch from the cephalic to the basilic vein and vice versa. A large antecubital vein also provides a suitable outflow for primary insertion and subsequent revisions. If necessary, there should be no hesitation to cross the elbow joint in search of a suitable outflow vein, as joint crossing does not seem to affect patency.[8] Others have noted inferior patency[3] with patch venoplasty compared to the jump graft with new venous anastomosis. On the relatively infrequent occasions of stenosis of the graft at the arterial anastomosis, revisional procedures are simple and easily effected. Most primary insertions and revisions are accomplished under local anesthesia as an outpatient procedure.

In our experience and that of others,[3,9] the incidence of infection in dialysis grafts appears distressingly high. Infection leads to graft abandonment in a significant number and apparently recurs in at least some patients. It is not clear whether inattention to proper technique or inherent immune deficiency is responsible for this individual predilection. Even infection of the prosthesis can be managed with successful salvage of the graft if the infective process is relatively localized and extensive tunnel infection is absent. In some renal dialysis patients, even extensive tunnel infection may present with little outward signs of inflammation or tenderness. Despite close physical examination, such grafts may appear completely normal. Because of this experience, we tend to explore aggressively and to ligate grafts when evidence for bacterial seeding is present. Even when a tunnel infection was not encountered, ligation of the graft has resulted in cessation of the bacteremia in a few instances, suggesting suture line seeding.

While ligation usually results in immediate improvement in the status of the patient, the focus of infection must usually be excised eventually. In an occasional patient, septicemia has persisted despite ligation of the graft and was relieved only when the graft was completely excised and removed. The surprisingly large number of access devices salvaged from localized infection by bypass was gratifying. Results appear to have been equally good whether the bypass was primary or secondary. The choice between these two techniques resides primarily on the status of the graft site during drainage. If significant cellulitis of surrounding tissue is present, a secondary bypass followed by initial incision and drainage is appropriate. Primary bypass is useful for a very localized inflammatory process or for chronic and indolent sinuses.

Pseudoaneurysms are a frequent complication of PTFE grafts. Many of these occur in long-standing grafts subjected to repeated puncture and injury. An element of venous obstruction from stenosis is present in many, potentiating the false aneurysm from high pressure in the graft.[10] Despite careful instruction to the contrary, some patients tend to stick the PTFE graft through the same needle tract, exacerbating this complication. Revision of the false aneurysm and replacement with a segment of fresh graft is relatively easy. It has been our experience that the technique is made considerably easier by using a tourniquet for vascular control, rather than circumferential dissection for clamp application. In fact, in most other revisional surgical procedures involving the PTFE graft, either tourniquet, digital, or Fogarty vascular control is used as necessary to avoid circumferential dissection. Circumferential dissection has a potential for injury to the deep aspect of the graft and vessels and should be avoided when possible.

When the lifetime of a PTFE graft is finally expended from repeated and recurrent complications, a site in the forearm on the same or opposite side for secondary insertion should be easily achieved. Even among patients who have been on dialysis for 10 years or more, loss of site for access insertion has seldom occurred in our experience.

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Ornithine-alpha-ketoglutarate Improves Skeletal Muscle Protein Synthesis as Assessed by Ribosome Analysis and Nitrogen Use After Surgery

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Total parenteral nutrition (TPN) was given for 3 days after elective abdominal surgery. The control group (N = 9) received TPN only and one group of patients (N = 6) received TPN supplemented with ornithine-alpha-ketoglutarate (0.35 g/kg bw/day). Protein synthesis in skeletal muscle was assessed from the total ribosome concentration and the percentage of polyribosomes. In the control group the total concentration of ribosomes decreased after surgery by 23% ($p < 0.05$) and the percentage of polyribosomes decreased by 21% ($p < 0.01$), whereas in the ornithine-alpha-ketoglutarate group both variables remained unaffected. The cumulative urinary urea excretion was significantly larger in the control group than in the ornithine-alpha-ketoglutarate group ($p < 0.05$). The calculated nitrogen balance was negative in the control group on each day of the study ($p < 0.05$), but that of the ornithine-alpha-ketoglutarate group was not statistically different from zero. The results show that postoperative maintenance of muscle protein synthesis and a more effective nitrogen use was achieved by supplementing TPN with ornithine-alpha-ketoglutarate, 0.35 g/kg bw/day.

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IN NONMALNOURISHED ADULT patients, the immediate post-traumatic period is characterized by whole body protein catabolism and a negative nitrogen balance.[1] Nutritional support, including total parenteral nutrition (TPN), counteracts the nitrogen losses and improves the negative nitrogen balance without attaining equilibrium.[2,3] The postoperative nitrogen supply is influenced by increasing the total amount of nitrogen provided[4] or by increasing the proportion of branched chain amino acids given,[5,6] without reversing the negative nitrogen balance to positive values.

After trauma, protein metabolism is influenced differently in individual tissues; skeletal muscle is of special interest because it constitutes the largest protein reservoir in the human body.[7] Protein synthesis in skeletal muscle decreases after surgery,[3,8] whereas the rate of protein breakdown remains unaffected after surgery of a moderate magnitude.[8,9] Nutritional support does not seem to be sufficient to reverse these changes.[3,8]

Supplementation of TPN with ornithine-alpha-ketoglutarate has been shown to maintain nitrogen balance after abdominal surgery.[10] The characteristic postoperative increase in the intracellular concentrations of some essential amino acids in skeletal muscle is also counteracted by ornithine-alpha-ketoglutarate.[11] In this investigation following elective abdominal surgery, a control group of patients received TPN only. Another group, given TPN supplemented with ornithine-alpha-ketoglutarate, showed a lower cumulative urinary urea excretion and a maintenance of skeletal muscle protein synthesis as assessed by the concentration and size distribution of ribosomes compared with the control group.

Materials and Methods

Patients

Fifteen metabolically healthy patients admitted to the hospital for elective cholecystectomy participated in the study. Their voluntary consent was obtained after the study's purpose, procedure, and risks were explained. The study protocol was approved by the Ethics Committee of the Karolinska Institute, Stockholm, Sweden. The characteristics of the patients, along with the operating time and the postoperative blood loss, are given in

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Table 1. Premedication was given in the form of morphine-scopolamine and anesthesia was administered using pentothal, diazepam, fentanyl, pencuronium, and N_2O/O_2. As prophylaxis against postoperative thrombotic complications, 500 mL of dextran 70, 60 mg/mL (Macrodex, Pharmacia Infusion, Uppsala, Sweden), was given. Intercostal blocks using bupivacaine, 5 mg/mL (Marcain, Astra, Södertälje, Sweden), were administered to relieve postoperative pain and ketobemidone was given on request. No patients requiring replacement of blood products were included in the study.

Nutritional Support

The patients were given intravenous fluids, 35 mL/kg bw/day. During the surgical procedure, 25 mg/mL of glucose (Rehydrex, Pharmacia Infusion) was infused. TPN included 0.2 g N/kg bw/day given as a balanced amino acid solution (Vamin-Glukos, KabiVitrum, Stockholm, Sweden) and 135 kJ/kg bw/day was supplied as equal parts of fat (Intralipid, KabiVitrum) and carbohydrate (Glukos, 100 mg/mL, Pharmacia Infusion). The nutrition was supplemented with electrolytes, trace elements (Addex-Kalcium Spår, Pharmacia Infusion), and vitamins (Vitalipid Adult and Soluvit, KabiVitrum). On the day of operation, half the nutritional regimen was administered.

The patients were randomized into two groups. The control group (N = 9) followed the TPN regimen previously described and the ornithine-alpha-ketoglutarate group (N = 6) was given the TPN regimen supplemented with ornithine-alpha-ketoglutarate, 0.35 g/kg bw/day (Ornicetil, Laboratoires Jaques Logeais, Paris, France). This amount of ornithine-alpha-ketoglutarate contains 0.01 g/kg bw/day of nitrogen, which was included in the calculation of the nitrogen balance but was disregarded as a nitrogen source with regard to the comparability of the two groups. The caloric content of 0.35 g of ornithine-alpha-ketoglutarate is approximately 5 kJ, which was regarded as neglectable as an energy source in the calculations.

Ribosome Analysis

The method for analyzing the ribosomes from skeletal muscle has been described in detail previously.[12] Muscle biopsy specimens of 50 mg wet weight were taken by the percutaneous needle technique after local anesthesia of the skin.[13] The specimens were frozen in liquid nitrogen within 2 minutes and then stored at −80 C for less than 2 weeks before analysis. The biopsy specimens were homogenized in a medium containing an RNase inhibitor. After centrifugation at 1500 × g for 10 minutes, the pellet was saved for the determination of DNA. The supernatant was ultracentrifuged at 102,000 × g for 2 hours in a 40.2 rotor (Beckman Instruments, Palo Alto, CA). The ribosome pellet obtained was suspended in medium. A portion of the suspension was layered onto a linear density gradient between 0.4 and 1.5 M sucrose. After centrifugation in a SM 50.1 rotor (Beckman Instruments) for 60 minutes at 149,000 × g, the gradient was pumped through a continuous flow cuvette and the absorbency was monitored at 260 nm. The area under the absorbency curve was determined. The total ribosome concentration was determined from the absorbency at 260 nm. The concentration was expressed as optical density (OD) units per milligram of tissue DNA. The DNA content was analyzed by a fluorometric method[14] using salmon DNA as a standard.

TABLE 1. *Characteristics of Patients and Surgical Procedure (Mean ± SEM)*

	Control Group	Ornithine-alpha-ketoglutarate Group
Sex (female/male)	5/4	4/2
Age (years)	58 ± 4	58 ± 6
Height (cm)	171 ± 4	168 ± 4
Weight (kg)	70 ± 4	69 ± 6
Operating time (min)	86 ± 15	102 ± 12
Peroperative blood loss (mL)	210 ± 30	180 ± 40

Urea Excretion and Nitrogen Balance

Urine was collected in 24-hour portions and assayed for urea.[15] The serum concentration of urea was determined daily and it varied less than 2 mmol/L; hence, the total urea pool of the patients was considered constant since there was no change in their body weight during the study. The nitrogen balance was calculated using the approximation suggested by MacKenzie,[16] estimating the nonurea urinary nitrogen losses to be 1.8 g/24 hours and the nonurinary nitrogen losses to be 1.7 g/24 hours.

Statistics

All values are given as mean ± SEM. Student's t-test for paired samples was used to compare different observations, and a two-way analysis of variance was used to compare the two different groups.[17]

Results

Skeletal muscle biopsies were performed immediately before the operation and on the morning of the third day after surgery. The ribosome fraction was isolated from the biopsy specimen and the concentration and size distribution of the ribosomes was determined. The percentage of polyribosomes was determined from the ribo-

TABLE 2. *Total Ribosome Concentration, Percentage of Polyribosomes, and Concentration of Polyribosomes in Skeletal Muscle of Patients Undergoing Elective Abdominal Surgery (Mean ± SEM)*

	Control Group	Ornithine-alpha-ketoglutarate Group
Total ribosome concentration (OD/mg DNA)		
Before surgery	49.2 ± 5.6	40.0 ± 4.7
After surgery	37.5 ± 4.4*	42.5 ± 3.5†
Percentage of polyribosomes		
Before surgery	50.6 ± 1.5	52.3 ± 2.7
After surgery	39.0 ± 3.3‡	53.2 ± 1.8§
Polyribosome concentration (OD/mg DNA)		
Before surgery	23.4 ± 2.9	20.9 ± 2.6
After surgery	14.5 ± 2.5‖	22.6 ± 1.9§

*$p < 0.01$, ‡$p < 0.05$, ‖$p < 0.001$ compared with preoperative values; †$p < 0.05$, §$p < 0.01$ compared with control group.

TABLE 3. *Daily Urinary Urea Excretion and Calculated Nitrogen Balance in the Period Immediately Following Elective Abdominal Surgery (Mean ± SEM)*

	Control Group	Ornithine-alpha-ketoglutarate Group
Urinary urea excretion (mmol/24 hr)		
Postoperative Day 1	278 ± 36	89 ± 28
Day 2	464 ± 46	500 ± 82
Day 3	486 ± 32	404 ± 46
Calculated nitrogen balance (g/24 h)		
Postoperative Day 1	−4.3 ± 1.0	0.9 ± 0.8
Day 2	−2.5 ± 1.3	−3.7 ± 2.3
Day 3	−3.1 ± 0.9	−1.0 ± 1.3

some profile, where the area under the curve is proportional to the amount of ribosome particles of different mass. The percentage of polyribosomes out in the total number of ribosomes decreased by 21% on the third day after surgery compared with the initial values in the control group ($p < 0.05$). No such decrease was demonstrated in the ornithine-alpha-ketoglutarate group (Table 2). The alteration was significantly different between the two groups on the third postoperative day ($p < 0.05$).

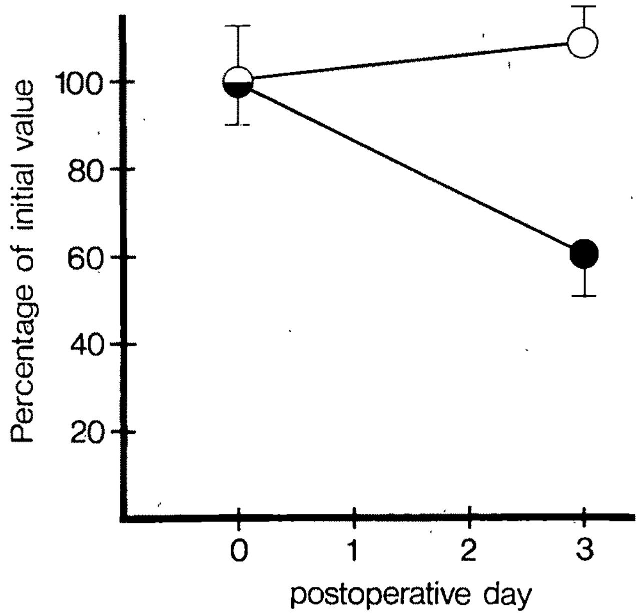

FIG. 1. The polyribosome concentration in skeletal muscle before surgery and on the third postoperative day in patients undergoing elective abdominal surgery. Patients received TPN (N = 9, filled circles) or TPN supplemented with ornithine-alpha-ketoglutarate (N = 6, open circles). The values are expressed as percentage of the original values noted before surgery. In the control group, the polyribosome concentration decreased significantly ($p < 0.001$). There was no postoperative decrease in the ornithine-alpha-ketoglutarate group. On the third postoperative day there was a significant difference between the two groups ($p < 0.01$). Values are given as mean ± SEM.

A comparison of the pre- and postoperative conditions in the control group showed a decrease in the total concentration of ribosomes per milligram of DNA by 23% on the third day after the operation ($p < 0.01$; Table 2). In the ornithine-alpha-ketoglutarate group no difference between the values was noted before and after surgery. On the third day following surgery the changes were significantly different between the two groups ($p < 0.05$). The concentration of polyribosomes per milligram of DNA was calculated from the total concentration of ribosomes and the percentage of polyribosomes. In the control group there was a 38% decrease in the polyribosome concentration between the original value and that of the third postoperative day ($p < 0.001$; Table 2). In contrast, the ornithine-alpha-ketoglutarate group showed no change in the polyribosome concentration 3 days after surgery (Fig. 1). On the third day after surgery the difference between the two groups was highly significant ($p < 0.01$).

Urinary urea was analyzed in 24-hour portions (Table 3). There was a significant larger cumulative excretion during the initial 3 days after surgery in the control group compared with the ornithine-alpha-ketoglutarate group ($p < 0.05$). Nitrogen balance was calculated from the urinary excretion of urea as presented in the Materials and Methods section. In the control group the nitrogen balance was negative on each day of the study ($p < 0.05$; Table 3). In the ornithine-alpha-ketoglutarate group the nitrogen balance was not statistically different from zero on any of the first 3 days after surgery. The cumulative nitrogen balance was calculated for the initial 3 postoperative days (Fig. 2). The difference between the two groups became statistically significant on day 3 after surgery ($p < 0.05$).

Discussion

Protein metabolism was evaluated by ribosome analysis. The total concentration of ribosomes is interpreted as a measure of the capacity for protein synthesis.[18,19] A high content of polyribosomes corresponds to a high rate of protein synthesis.[20] Hence, the percentage share of polyribosomes is a measure of the activity of protein synthesis. Especially when several consecutive samples are available, changes in protein synthesis activity can be studied over a prolonged period.[12,18,21] The reproducibility of total ribosome concentration per milligram of DNA and the percentage of polyribosomes is approximately 6% in both cases when the current technique is used.[22]

Protein synthesis in skeletal muscle was assessed from the total concentration and size distribution of ribosomes. Applied to human muscle tissue, this technique shows a decrease in both variables after elective abdominal surgery, regardless of whether TPN is given in the immediate postoperative period.[3] An isonitrogenous amino acid solution enriched with branched-chain amino acids cannot prevent this decrease.[6] Supplementation of a standard TPN program with ornithine-alpha-ketoglutarate prevented the fall in both the total ribosome concentration and the percentage of polyribosomes. These findings are in accordance with the normalization of the intracellular concentrations of free branched chain and aromatic amino acids seen after surgery.[11] The preserving effect of ornithine-alpha-ketoglutarate on whole-body nitrogen economy, as indicated by the improvement in nitrogen balance, confirmed previous results.[10]

The mechanism for the nitrogen sparing effect of ornithine-alpha-ketoglutarate is not clear. Supplementation of TPN with ornithine has no beneficial effect on nitrogen economy after surgery (E. Vinnars, unpublished results). One hypothesis is that alpha-ketoglutarate, being the corresponding ketoacid to glutamic acid, can counteract the increase seen after trauma in nitrogen efflux from the periphery to the splanchnic area. Ornithine-alpha-ketoglutarate, 0.022 g/kg bw/h, given for 150 minutes to healthy male volunteers after an overnight fast, does not affect the efflux of amino acids from peripheral tissue.[23] The effect on amino acid flux in patients in protein catabolic states remains an open question. To improve nitrogen use and to benefit from the nitrogen sparing effect, ornithine-alpha-ketoglutarate possibly should be given with a nitrogen supply.

The balanced amino acid solutions that are commercially available do not include glutamine, and the content of glutamic acid is limited by its tendency to evoke nausea when given in high concentrations. The alpha-ketoglutarate included as ornithine-alpha-ketoglutarate presumably provides enough carbon skeletons to compensate for a shortage of glutamine/glutamic acid in the commercially available amino acid solutions. In animal experiments, post-traumatically administered glutamine prevents the profound decrease in the intracellular free glutamine concentration in skeletal muscle seen otherwise,[24] and the overall nitrogen economy is improved. Ornithine-alpha-ketoglutarate given to patients undergoing colonic resection does not prevent the decrease in the intracellular concentrations of free glutamine.[11] In animals both the influx of branched chain amino acids and the total intracellular free amino acid nitrogen are correlated to the efflux of amino acid nitrogen from peripheral tissue after surgery. To determine if a shortage of glutamine is the critical point in post-traumatic protein catabolism, it seems reasonable to give glutamine to human subjects also. The pharmaceutical difficulty involved in preparing a stable glutamine solution remains a crucial problem. The dipeptides currently available for research purposes may be another future source in this context.

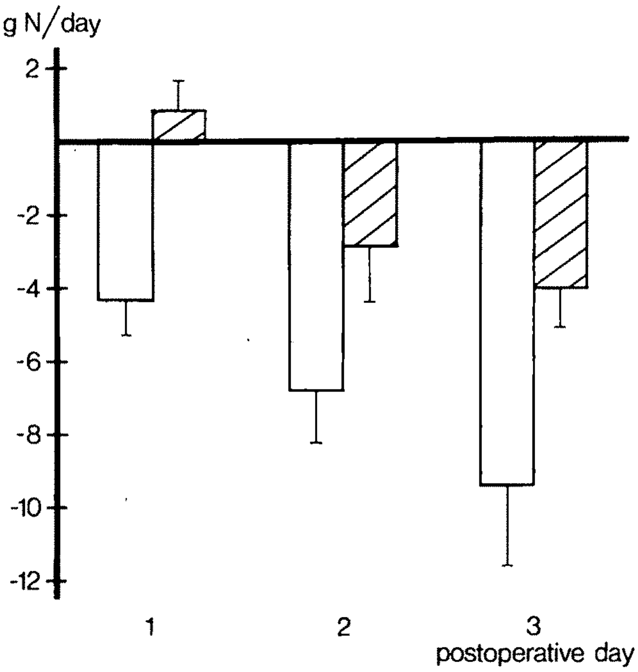

FIG. 2. The cumulative calculated nitrogen balance on days 1–3 immediately after elective abdominal surgery. Patients received TPN (N = 9, open bars) or TPN supplemented with ornithine-alpha-ketoglutarate (N = 6, hatched bars). There was a significant difference between the two groups on each day ($p < 0.05$). Values are given as mean ± SEM.

In conclusion, after elective abdominal surgery, TPN supplemented with ornithine-alpha-ketoglutarate prevented the decrease in skeletal muscle protein synthesis normally observed with TPN only and diminished urinary urea excretion. The findings suggest the use of ornithine-alpha-ketoglutarate as a supplement to nutritional support after major surgery and in septic patients. The mechanisms underlying the nitrogen sparing effect of ornithine-alpha-ketoglutarate are not clear and require further investigation.

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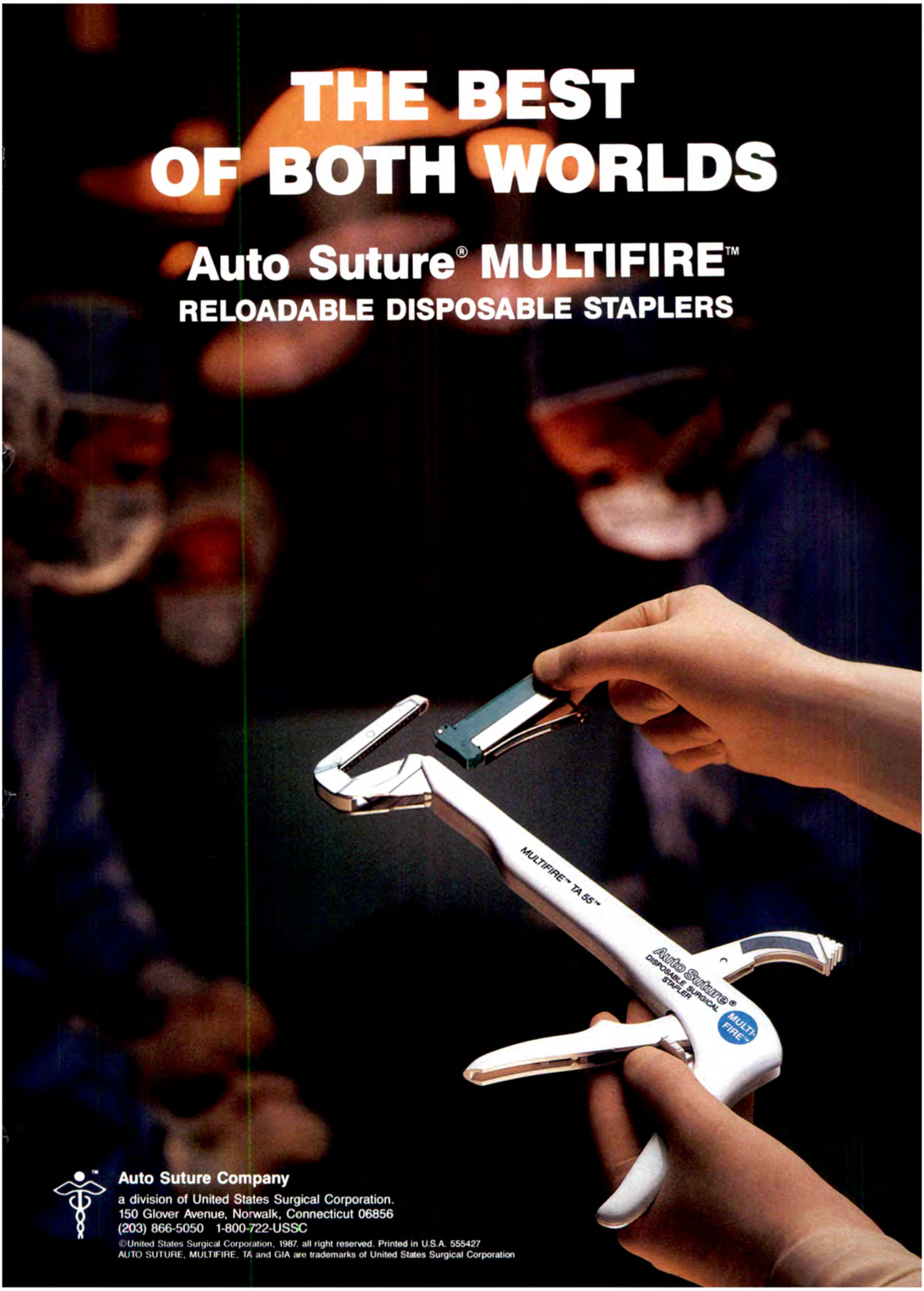

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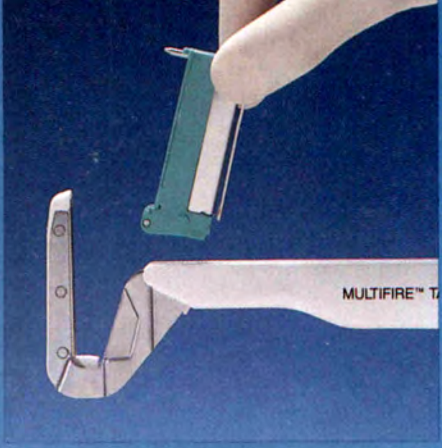

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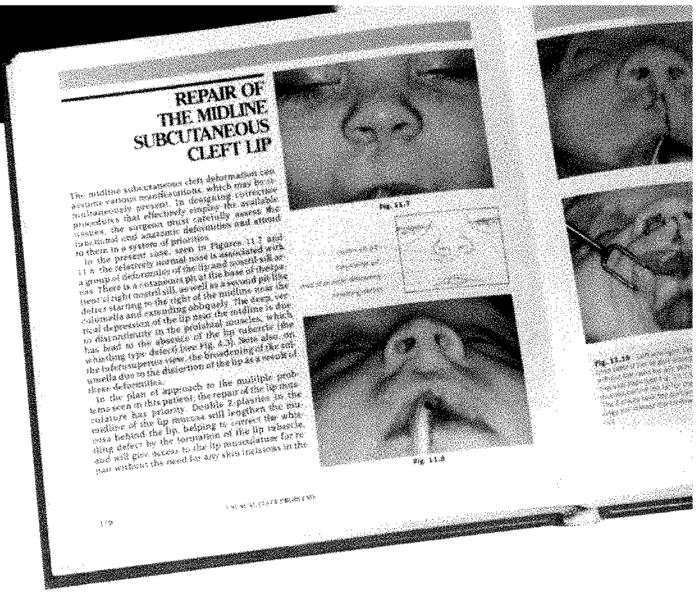

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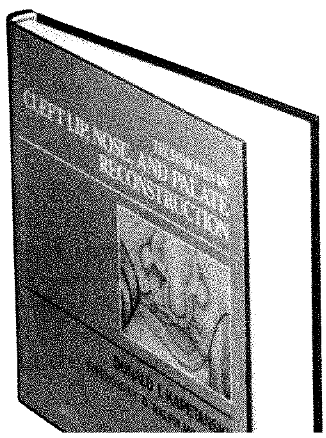

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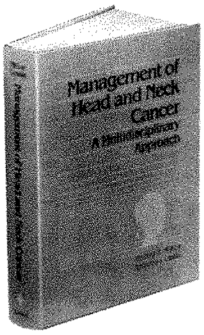

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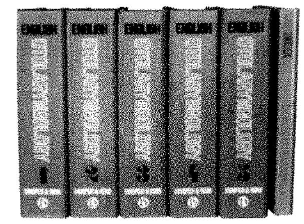

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Book Reviews

William P. Longmire, Jr., M.D.
Advisor for Editorial Board
Los Angeles, California

H. Kim Lyerly, M.D.
Advisor for Residents in Surgery
Durham, North Carolina

Surgery of the Gallbladder and Bile Ducts. Lawrence W. Way, Carlos A. Pellegrini. 700 pp. Philadelphia: W. B. Saunders Co. 1987. $85.00.

THIS IS A COMPREHENSIVE BOOK that consists of 43 chapters spanning 676 pages and a 24 page index. It covers almost every aspect of biliary tract disease as well as pertinent physiology and pathophysiology. Fifty authors contribute their expertise and insight. With few exceptions, the chapters are remarkably uniform in their approaches. In addition to the traditional subjects, there are chapters dealing with parasites and infestations, fistula, pediatric problems, and even trauma. One can only quibble with certain minor omissions. Someone not completely familiar with the field may have difficulty in trying to decide what is the best approach to treating a particular biliary tract problem, for the style of the book is directed at a fairly knowledgeable audience. The latter will appreciate its depth. The chapters are particularly well referenced.

Not all of the chapters approach certain aspects from the point of view that there is controversy; those that do are masterful. The neophyte may have a problem knowing that controversy exists and that a particular author's view represents an extreme bias, but the information presented serves as a solid foundation for exploring the original literature. Those sections dealing with the technical aspects of surgery contain the usual amount of dogma. Near perfection would have been achieved had the authors given the historical and physiologic or rational bases or more comprehensive explanations for certain operative approaches or details. Even these omissions, however, do not detract from enjoying the crisp, informative style of the chapters. This is a book for surgeons and gastroenterologists alike, but not for someone looking for the nuances of the technical aspects of biliary tract surgery. Would I buy it? Yes, it's a new standard reference.

DAVID FROMM, M.D.
Syracuse, New York

Atlas of Advanced Surgery. Martin S. Litwin. 198 pp. New York: Yorke Medical Books. 1986. $95.00.

FULFILLING THE EDITOR'S PLAN, 42 authors contributed 37 chapters on surgery of the enteric and splanchnic venous systems to this attractive book so that ". . . the reader has ready access to contemporary descriptions of these operations in a clearly illustrated way that does not necessitate a literature search." Sampling a quarter of the articles shows the array: Ellis, *Esophagogastrectomy;* Urschel, *[Esophageal] Diversion and Exclusion . . .*; Thal, *Fundic Valvuloplasty . . .*; Hill, *Hiatal Herniorraphy. . .*; Longmire, *Intrahepatic Cholangiojejunostomy. . .*; Calne, *Hepatic Resection;* Jones, *Transduodenal Sphincteroplasty;* Litwin, *Pancreaticoduodenectomy;* Kock, . . . *Continent Ileostomy;* Localio, *Abdominosacral Resection*. . . . The typography is clear. Original and adapted renditions by a single artist lend desirable consistency.

In redaction the publishers have done less well. Typographic errors begin in the preface. 'This' is frequent as a pronoun without an antecedent. Superfluous 'It. . . that' clauses begin sentences. Orotund and self-evident statements are permitted. Some units of measure are nonstandard or obsolete: gm for gram; 0.5 needle; # 40 French in one part, no. 40 French in others. 'Pancreatico-' is confused with 'pancreato-.' Some trade names are capitalized, others not.

The question a potential buyer might ask is, "What is 'advanced' surgery?" Although some topics included in *Zollinger and Zollinger* are also to be found in this book, complex vascular and endocrine surgery are not. This is a fine reference in alimentary tract surgery for chief residents and stages beyond.

RONALD A. MALT, M.D.
Boston, Massachusetts

Surgery of Coronary Artery Disease. D. J. Wheatley. 676 pp. St. Louis: The C. V. Mosby Co. 1986. $79.95.

SINCE CORONARY ARTERY bypass surgery became an acceptable clinical procedure, a vast amount of literature has been written addressing the subject. Numerous attempts to assimilate, organize, and condense this large amount of material into a comprehensive teaching and reference text have met with a wide array of results. Few have been as successful in attaining this monumental task as has D. J. Wheatley in *Surgery of Coronary Artery Disease.*

This text represents a comprehensive manuscript "intended primarily for the trainee and practising cardiac surgeon." Beginning with a detailed historic review of the subject, it outlines completely the entire scope of patient management, including up-to-date diagnostic modalities, indications for medical therapy, and newer invasive medical techniques (percutaneous transluminal coronary angioplasty and intracoronary thrombolysis). The entire scope of surgical treatment, including preoperative assessment, operative technique, and postoperative care is thoroughly reviewed, and the management of associated complications and concomitant illnesses discussed.

The contributing authors represent a roster of many of the world's outstanding cardiovascular physicians in their particular field. The list of references following each chapter is extensive, well-organized and complete.

Some of the illustrations obtained from coronary angiography are not clear, and a number of those in the text could have been eliminated without detracting from its overall content. The information rendered by various contributing authors at times overlaps in subject matter. Lacking is a chapter dealing with the treatment of end-stage coronary ischemia and myocardial failure, including the use of mechanical support devices and cardiac transplantation. However, these deficiencies are minor when compared with the overall superiority of the text.

I second the opinion of Dr. Denton A. Cooley, who states in the Foreword of the text: "This elegant book is a careful, studious approach to the surgical treatment of coronary artery disease . . . and will be a reference of inestimable value both to cardiologists and cardiovascular surgeons as they meet the needs of patients with coronary artery disease."

KENT W. JONES, M.D.
Salt Lake City, Utah

A Colour Atlas of Gastrointestinal Endoscopy. K. F. R. Schiller, Roy Cockel, Richard H. Hunt, with the collaboration of B. Sterry Ashby, Giles W. Stevenson. 240 pp. Philadelphia: W. B. Saunders Co. 1987. $110.00.

GASTROINTESTINAL ENDOSCOPY is a visual procedure. Although the final diagnosis should be based on histopathology, pattern recognition of lesions and the detection of abnormality (to prompt taking biopsies) are of primary importance. It is therefore surprising that few atlases of normal and abnormal appearances have been published, despite the wealth of experience throughout the world over the last 20 years and the billions of photographs that have been taken.

The scarcity of atlases reflects the size of the task in assembling a comprehensive selection of good quality pictures, encompassing all areas of the gastrointestinal tract and its diseases.

This atlas certainly succeeds in its aim, to provide a manual for less experienced endoscopists and a reference source for the experienced. The photographs are generally of high quality. There are some exceptions where the rarity of the lesions, or the excitement of the occasion, may have affected the outcome. Thus, some illustrations of rarer types of polyps and of emergency procedures in bleeding patients are less than ideal. Experts will review these pictures carefully to see if they disagree with any interpretation. The pancreatogram illustration of "minimal change pancreatitis" might be interpreted as more severe disease by some. We question the description of the common periampullary diverticulum as "congenital" and do not like the described method for placing a feeding tube, which appears to involve passing the endoscope with the forceps protruding from the tip. There are some minor errors in the references. The line drawings, although of good quality, add little to the clarity, since they are not annotated.

This atlas should be available in all areas where endoscopy training programs are pursued, and many individual gastroenterologists will wish to have a personal copy.

PETER B. COTTON, M.D.
Durham, North Carolina

Letters to the Editor

November 21, 1986

Dear Editor:

Drs. Rotstein, Pruett, and Simmons[1] demonstrated that fibrin deposition by peritonitis significantly impairs phagocytosis of bacteria by neutrophils enmeshed in fibrin, and that contaminated fibrin predispose to residual abscess formation even if an adequate number of normal leucocytes were present.

Considering that fibrin deposition blocks the action of parenterally administered antibiotics because of its lack of vascularity, and that it is at the same time the main cause of early and late intestinal obstructions (due to the anarchical arrangement of bowel loops), there is every reason to admit that the removal, in some way or another, of this fibrino-purulent coat would constitute an essentially therapeutic approach in the treatment of acute septic peritonitis.

Hudspeth[2] resorted to the so-called "radical surgical debridement," employing a scrupulous cleansing procedure of the entire peritoneal surface "by forceps and gentle dissection," but the author himself qualifies this procedure as tedious and time-consuming (average operating time 3 hours). This type of operation was viewed with skepticism and did not gain acceptance.

Polk and Frey[3] did a randomized, prospective comparison study between radical peritoneal debridement (RPD), of Hudspeth type, and standard surgical management of peritonitis, concluding that RPD shows no benefit in survival nor reduction of frequency of reoperation between the two treatment groups, and that data further suggest that elderly patients tolerate radical peritoneal debridement poorly, as indicated by uniform death of patients over 60 years of age in the RPD group.

At the discussions about this study at the 100th Annual Session of the American Surgical Association (Atlanta, April 23–25, 1980), the speakers[3] qualified RPD as: a disastrous approach; risk of spreading the infectious process and increase of paralytic ileus; difficult job to remove all the exudate, particularly in some of the recessed pockets and spaces of the peritoneal cavity, such as the subphrenic areas and the lesser peritoneal sac.

Starting in the early 1960s, I employed in a series of patients with peritonitis an enzymatic debridement, utilizing freshly (ad hoc) prepared solutions of crystallized trypsin or chymotrypsin in isotonic saline: by gently wiping with a pad soaked in this solution, it is possible to remove quite easily, quickly and atraumatically the fibrino-purulent pseudo-membranes without bleeding or visceral trauma, especially to the intestines. To prevent a prolonged enzymatic action upon the peritoneum, the respective field is intermittently irrigated with isotonic saline (at body temperature). At the end of the procedure, before closing the abdomen, one irrigates again systematically and abundantly the abdominal cavity. Proceeding in this manner, I achieved in some cases startling results with respect to survival, and in others a remarkable lack of major complications (recurrent abscess formation, intestinal obstructions).

Due to reasons beyond my control, I was unable to conduct any experimental studies pertaining to systemic or local side effects, to the optimal enzymatic concentrations, or to the utilization of other proteolytic enzymes/(new substances?), but I do believe that this approach could be (for the interested in this problem) an object of investigation.

VICTOR E. MUNTEAN, M.D.
Stuttgart, West Germany

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April 9, 1987

Dear Editor:

Thank you for the opportunity to reply to Dr. Muntean's letter. The three major defense mechanisms comprising the body's response to bacterial soiling of the peritoneal cavity are: (1) mechanical clearance of bacteria *via* the diaphragmatic lymphatics, (2) influx of phagocytic cells (initially macrophages and then neutrophils), and (3) sequestration of bacteria by fibrin deposition.[1] The consequences of bacterial sequestration by fibrin appear to be somewhat paradoxical. In the initial phases of peritonitis, fibrin plays an important role in preventing the systemic spread of bacteria, thereby reducing the mortality associated with a large bacterial inoculum into the peritoneal cavity.[2,3] However, studies from several laboratories, including our own, have demonstrated that the infected fibrin sequestrum can act as a nidus for residual infection and subsequent abscess formation.[2–4] Thus, the scientific rationale for debridement of fibrin (either mechanical or enzymatic) as a means of preventing abscess formation is well based.

Both heparin and low molecular weight dextran have been shown to be capable of preventing abscess formation and improving survival in animal models of intra-abdominal infection (usually intestinal devascularization).[5–7] In the single reported study in which intra-abdominal abscesses were initiated by enmeshing bacteria with a fibrin clot, heparin and heparin fractions without anticoagulating properties failed to prevent abscess formation.[8] The use of fibrinolytic agents as suggested by Dr. Muntean has been tested by Rodeheaver et al.[9] in a wound infection model. These authors demonstrated that several fibrinolytic agents were able to obviate subcutaneous infection initiated by an infected plasma clot. Further rationale for the use of fibrinolytic agents is gained from examining peritoneal adhesions as an analogy for abscess formation. Their pathogenesis derives from sterile fibrin exudates, which act as matrices for collagen deposition and subsequent adhesion formation.[10] Experimentally, adhesions have been prevented with the fibrinolytic agents streptokinase and urokinase, which act by converting plasminogen to plasmin.

Prevention of abscess formation following surgery for diffuse peritonitis would contribute significantly to the reduction of morbidity and mortality in this disease. The ideal fibrinolytic agent must act locally in the peritoneal cavity, should cause minimal local tissue trauma, and should effect gradual dissolution of the infected nidus so that the beneficial sequestering action of fibrin will not be lost. Studies examining different fibrinolytic agents in this role are presently being performed by one of the authors (O. R.). The rationale for these studies are echoed in Dr. Muntean's letter.

O. D. ROTSTEIN
Toronto, Ontario
T. L. PRUETT
Charlottesville, Virginia
R. L. SIMMONS
Pittsburgh, Pennsylvania

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March 18, 1987

Dear Editor:

In their article, "Jejunal Interposition for Benign Esophageal Disease," C. Wright, M.D., and A. Cuschieri, M.D., in Ann Surg 1987; 205:54–60, describe their procedures in 30 patients, 21 of which were for intractable reflux stricture. The surgery for these 21 procedures deals with the end result of a pathologic process, not with the basic cause. It was also accompanied by 25 significant complications. The basic cause of reflux may still remain. If the stricture can be dilated, antrectomy and Roux-n-Y gastroduodenostomy results in cessation of reflux and no further stenosis.[1–4] Is it possible that the incidence of carcinoma of the gastric pouch would be less than the 4.5-fold increase reported after 20 years, with diversion of bile with the Roux-en-Y?[2] McCallum et al.,[5] have shown that gastric emptying of an isotope-labeled semisolid meal was delayed in 41% of patients with gastroesophageal reflux. This could result in distraction of the gastric wall and the valvuloplasty with return of reflux.

It is interesting to note that Nissen may have recognized the causative factor of reflux in small hiatal hernias and in reflux without hiatal hernia, where he found the angle of His was obtunded. Here he did both an anterior gastropexy and a fundoplication.[6] The loss of the angle of His may be early evidence of poor gastric emptying and distraction of the gastric wall.

Kim and Malagelada[7] have described a pacemaker present in the distal greater curvature of the stomach that regulates gastric emptying. Bradygastria, tachygastria, and arrhythmia may upset the normal 3 cycles/minute of the pacemaker, resulting in poor gastric emptying and antral dysfunction. Medical management with metaclopramide may be helpful. Rather than surgery, could there be a place for an implanted pacemaker responsive to gastric wall distraction?

LAWRENCE BRASLOW, M.D.
Riverside, California

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April 8, 1987

Dear Editor:

In reply to Dr. Lawrence Braslow's letter, oesophageal replacement with a jejunal loop, or for that matter colon, is recommended for disease that necessitates *excision* of the involved gullet. It is not recommended as the treatment for reflux disease. The high postoperative morbidity due largely to respiratory complications described in this series reflects the very high incidence of chronic obstructive airways disease and cigarette smoking in Scotland and is comparable to that encountered after major abdominal surgery in this country. The safety of the procedure is reflected by the one postoperative death (3.5%) that occurred in a patient in whom the oesophageal resection and jejunal replacement were performed as an emergency after severe rupture, complicating attempts at dilatation of an intractable stricture.

A. CUSCHIERI
Dundee, Scotland

April 23, 1987

Dear Editor:

Starr and Cornicelli[1] have reported a method to improve accuracy of central venous catheter placement in 84 patients presenting for cardiac surgery. Although of interest, their technique cannot be considered as a method of choice for two reasons.

First, the high incidence of serious, acute complications associated with the subclavian route for insertion of central venous catheters is well documented.[2] Indeed, the occurrence of subclavian artery punctures (3 patients), pneumothoraces (2 patients), and persistent skin bleeding (2 patients) in Starr's patients who were about to undergo cardiac surgery (presumably with positive-pressure ventilation and heparin administration) is a testament to the frequency of serious complications that are encountered with this approach. In practice, cannulation of the right internal jugular vein is preferable, and safer, prior to anticoagulation.[3]

Second, it seems anomalous to produce a minor complication (premature atrial contractions) to verify successful positioning of a central venous catheter. When accurate location of the catheter tip is mandatory, the standard methods to confirm position remain chest roentgenography, transduced pressure wave form, and P wave configuration on ECG with the saline-filled catheter functioning as a unipolar ECG lead.[4]

Richard H. Riley, M.B., B.S.
Neville J. Davis, F.F.A.R.A.C.S, F.F.A.R.C.S.
Nedlands, Australia

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May 20, 1987

Dear Editor:

Our recent paper describes the use of a floppy tip J-wire to deliberately induce PACs during CVP catheter placement, in order to ensure correct catheter tip location.

The letter from Dr. Riley and Dr. Davis contains two criticisms. The first relates to our use of the subclavian route, as opposed to the internal jugular or other route, for the successive introduction of the 18G needle, floppy tip guidewire, and catheter. The perennial subclavian/internal jugular controversy is moot to the point of the paper, since the guidewire technique can equally well be used with either of these methods. I concede that the weight of literature is in favor of the internal jugular route, but my personal feeling is that, in such an operator-dependent area, each doctor must use the method that gives him or her best results in terms of correct placement ratios, complications, and time spent on the procedure. However, the paper purposely did not pretend to enter this controversial area.

The second criticism relates to the anomaly of using deliberate induction of PACs to detect the presence of the J-wire tip in the right atrium. Perhaps the most challenging concept in our paper was the proposition that such PACs are in fact benign, and rather than being considered a complication, should be considered a signpost to the right atrium.

Lastly, our method was intended to supplement and not to replace the standard methods mentioned in the letter. Indeed it was our dissatisfaction with the existing methods (for technical or logistical reasons) that led us to look for a simpler and more reliable index of CVP catheter placement. My personal view is that, in hospitals blessed with an efficient and accurate x-ray department, an immediate chest x-ray is the procedure of choice for confirming correct CVP tip location. Thus the "procedure of choice" concept referred to above must depend on each hospital's strengths and weaknesses. Our paper merely introduced another methodology for the consideration of our colleagues.

David S. Starr, M.D.
Toledo, Ohio

April 20, 1987

Dear Editor:

Dunnington et al. report that jaundice in patients with alcoholic cirrhosis is rarely the result of cholelithiasis.[1] Almost 25 years ago, before the advent of ultrasound and radionuclide scans, similar conclusions were made in another study of alcoholic liver disease.[2] The axiom of that report seemingly remains valid: ". . . the performance of an exploratory operation in order to exclude common duct disease is not justified in the majority of cases."

The symptomatology and clinical findings in patients with alcoholic liver disease frequently simulates gallstone disease and it would have been informative if Dunnington and associates had included those laboratory and radiologic studies that prompted surgical intervention in the 22 patients. Because of the rarity of choledocholithiasis in cirrhotic subjects, ERCP is rarely necessary in my opinion.

It might interest Dr. Dunnington to learn that my study of alcoholic liver disease was prompted by a (world) renown surgeon who, during my presentation of such cases as the gastorenterology fellow, would frequently admonish me for failing to refer these patients to surgery since "we were overlooking gallstones and common duct obstruction." I am, of course, eternally grateful for his goading me into reporting my findings.

Lee R. Sataline, M.D.
Cheshire, Connecticut

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May 26, 1987

Dear Editor:

We appreciate Dr. Sataline bringing to our attention his fine article published in the *American Journal of Medicine* 25 years ago. This report approached the cirrhotic patient from a somewhat different perspective than ours, namely, the differential diagnosis of a biochemical abnormality, an elevated alkaline phosphatase value. Our report, however, discussed the problem of diagnosis and management of patients with documented cholelithiasis and symptoms consistent with acute cholecystitis or choledocholithiasis.

With regard to the indications prompting surgical intervention, we refer to Table 1 in our report, which states that most patients were explored for symptoms of biliary colic and/or acute cholecystitis. Ours was a retrospective review and, from what we have learned from this experience as well as from Dr. Sataline's review, we would hope that exploration could be avoided in a high percentage of these patients by using the algorithims we outlined. Although ERCP is rarely necessary, it is a useful adjunct in the patient with cholelithiasis and a dilated common duct by ultrasound. No other diagnostic study can so effectively rule out a common duct stone in this setting. It seems to us to be a more reasonable option than those available to Dr. Sataline when he reported his series of patients, *i.e.*, the use of liver biopsy or nutritional support in the hopes that symptoms of alcoholic hepatitis might resolve.

Gary Dunnington, M.D.
C. W. Putnam, M.D.
Tucson, Arizona

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David C. Sabiston, Jr., M.D.
Annals of Surgery
Department of Surgery
Duke University Medical Center
Durham, North Carolina 27710

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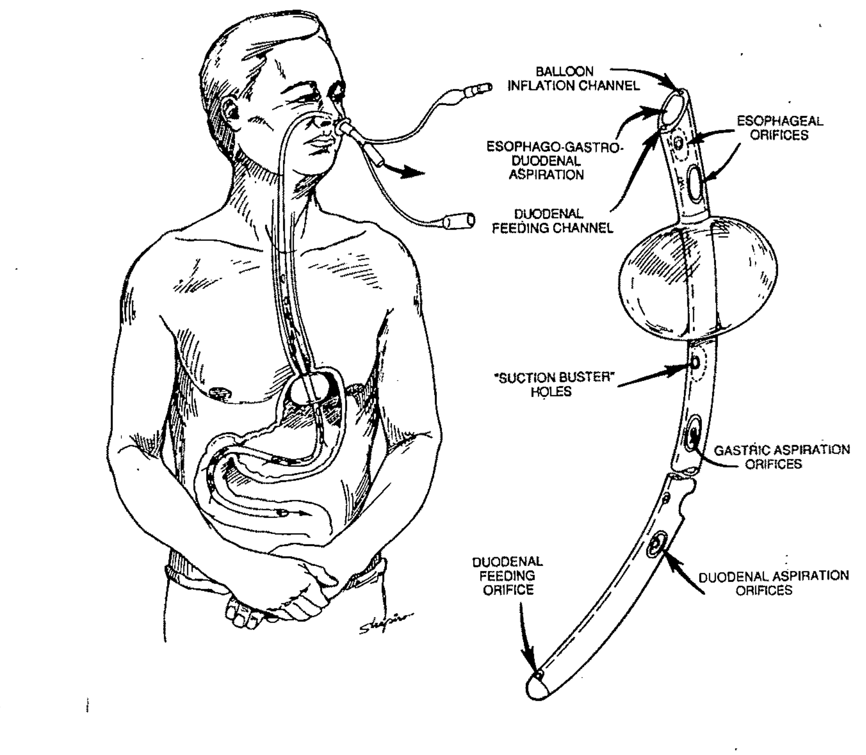
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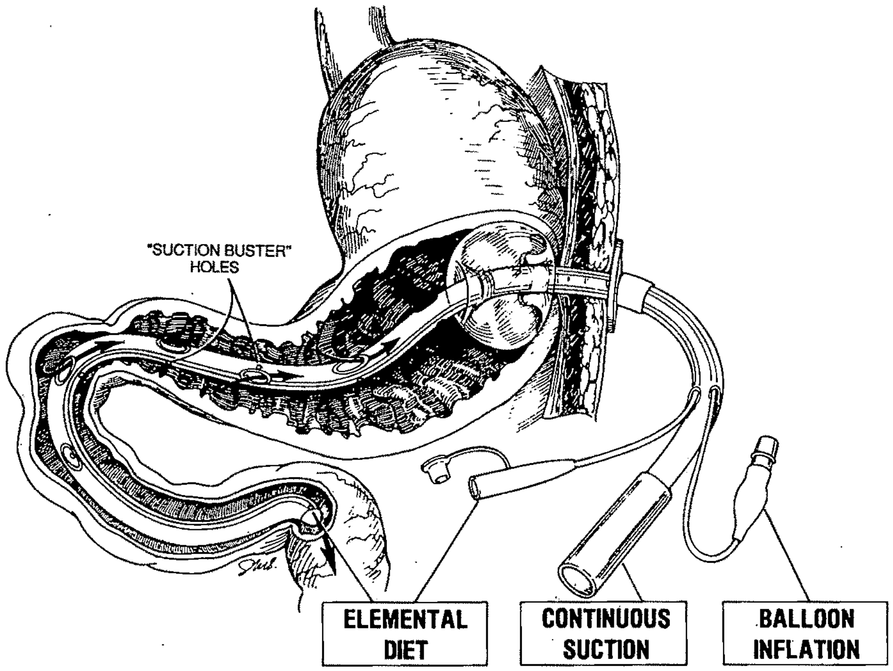

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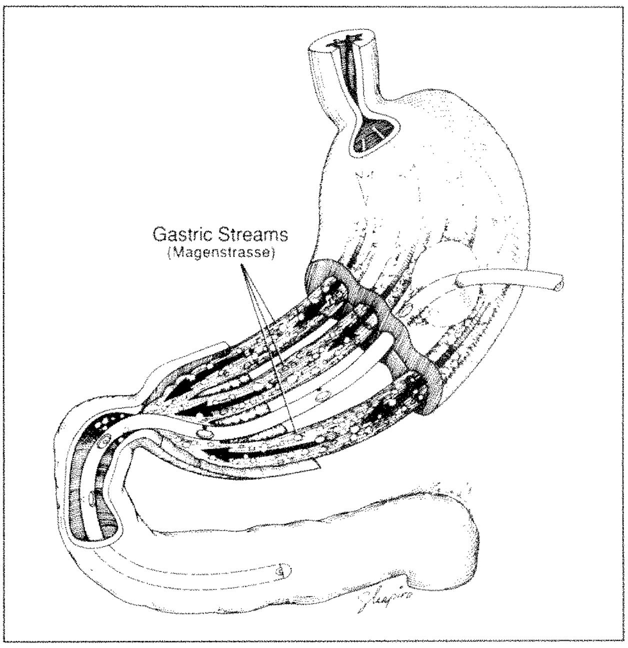

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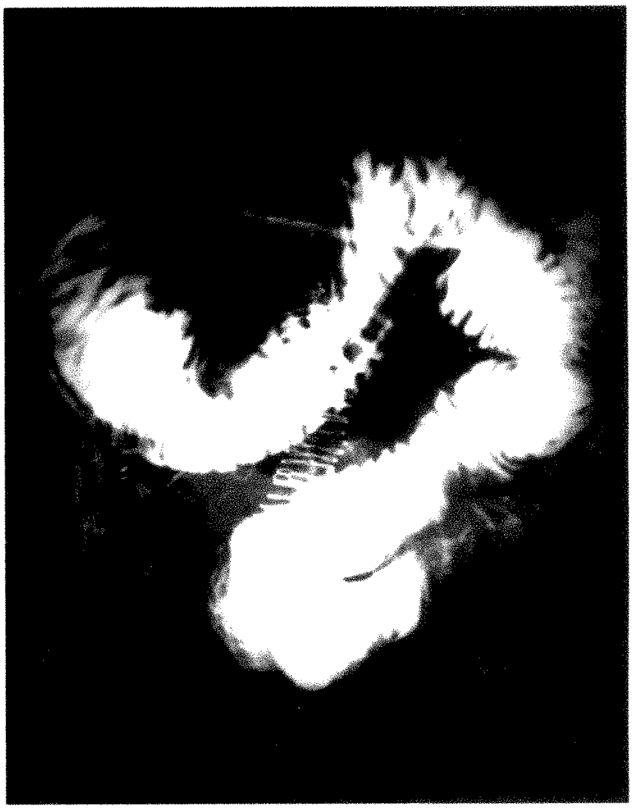

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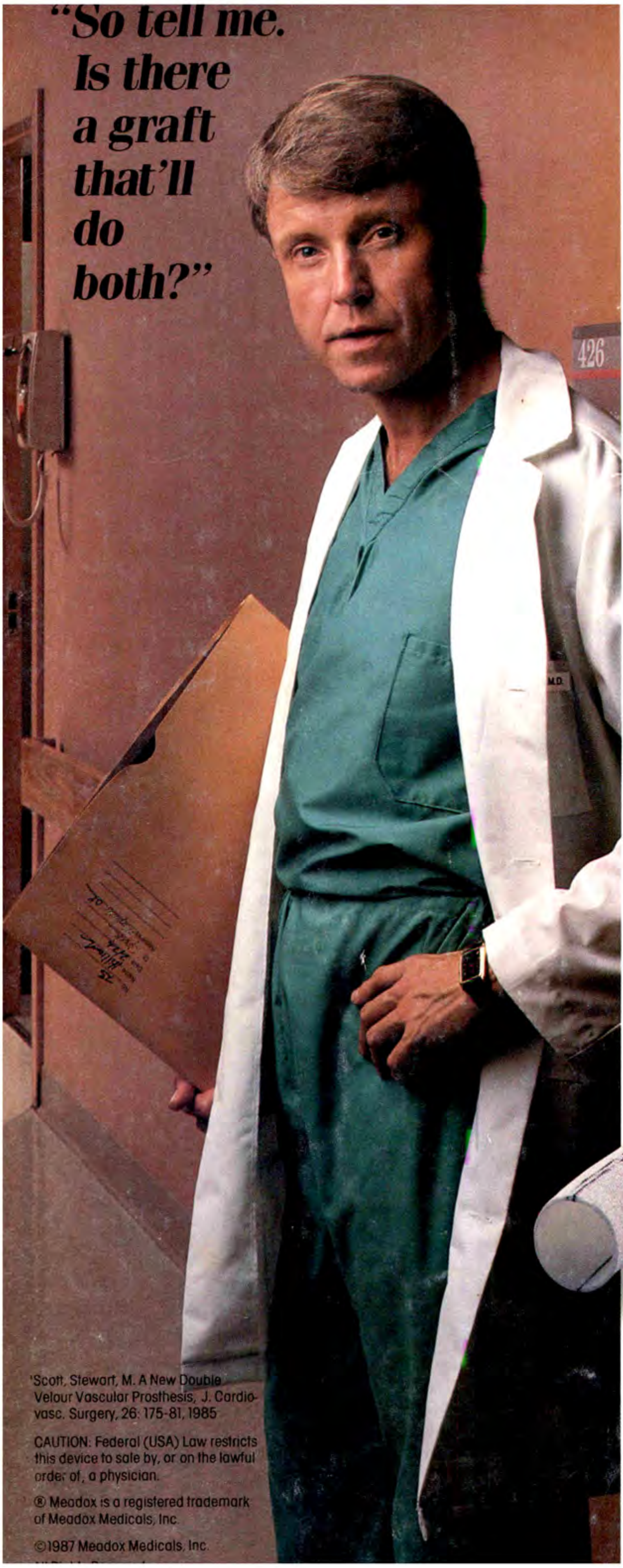

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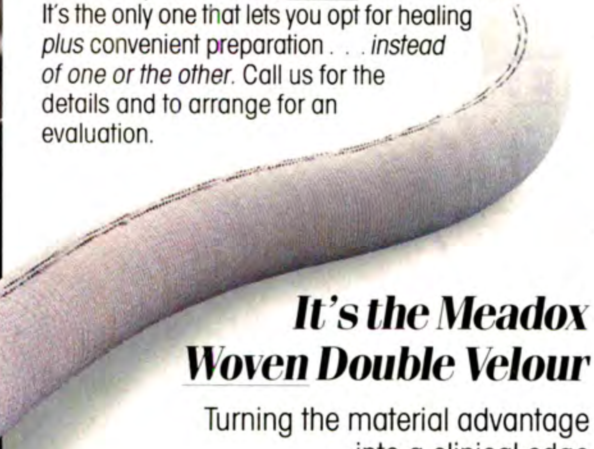

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[1] Scott, Stewart, M. A New Double Velour Vascular Prosthesis, J. Cardiovasc. Surgery, 26: 175-81, 1985

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Gynecologic infections caused by *Staphylococcus aureus*[†] (including penicillinase- and nonpenicillinase-producing strains), *Staphylococcus epidermidis*,[*] *Streptococcus* species (excluding enterococci), *E coli*, *Proteus mirabilis*, *Neisseria gonorrhoeae*, *Bacteroides* species (excluding *B distasonis*, *B ovatus*, *B thetaiotaomicron*), *Fusobacterium* species,[†] and gram-positive anaerobic cocci (including *Peptococcus* and *Peptostreptococcus* species[†]).

Intra-abdominal infections caused by *E coli*, *Klebsiella* species (including *K pneumoniae*[†]), *Streptococcus* species (excluding enterococci), and *Bacteroides* species (excluding *B distasonis*, *B ovatus*, *B thetaiotaomicron*).

Bone and joint infections caused by *Staphylococcus aureus*.[†]

[*] **NOTE:** Some strains of *Staphylococcus epidermidis* are resistant to cefotetan.

[†] Efficacy for this organism in this organ system was studied in fewer than ten infections.

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If there are signs and symptoms of infection, specimens for culture should be obtained for identification of the causative organism so that appropriate therapeutic measures may be initiated.

CONTRAINDICATIONS

CEFOTAN is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

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Before therapy with CEFOTAN is instituted, careful inquiry should be made to determine whether the patient has had previous hypersensitivity reactions to cefotetan disodium, cephalosporins, penicillins, or other drugs. This product should be given cautiously to penicillin-sensitive patients. Antibiotics should be administered with caution to any patient who has demonstrated some form of allergy, particularly to drugs. If an allergic reaction to CEFOTAN occurs, discontinue the drug. Serious acute hypersensitivity reactions may require epinephrine and other emergency measures.

Pseudomembranous colitis has been reported with the use of cephalosporins (and other broad-spectrum antibiotics); therefore, it is important to consider its diagnosis in patients who develop diarrhea in association with antibiotic use.

Treatment with broad-spectrum antibiotics may alter normal flora of the colon and may permit overgrowth of clostridia. Studies indicate a toxin produced by *Clostridium difficile* is one primary cause of antibiotic-associated colitis. Cholestyramine and colestipol resins have been shown to bind the toxin in vitro.

Mild cases of colitis may respond to drug discontinuance alone. Moderate to severe cases should be managed with fluid, electrolyte, and protein supplementation as indicated. When the colitis is not relieved by drug discontinuance, or when it is severe, oral vancomycin is the treatment of choice for antibiotic-associated pseudomembranous colitis produced by *C difficile*. Other causes should also be considered.

PRECAUTIONS

GENERAL: As with other broad-spectrum antibiotics, prolonged use of CEFOTAN may result in overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection does occur during therapy, appropriate measures should be taken.

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CEFOTAN should be used with caution in individuals with a history of gastrointestinal disease, particularly colitis.

INFORMATION FOR PATIENTS: As with some other cephalosporins, a disulfiram-like reaction characterized by flushing, sweating, headache, and tachycardia may occur when alcohol (beer, wine, etc) is ingested within 72 hours after CEFOTAN administration. Patients should be cautioned about the ingestion of alcoholic beverages following the administration of CEFOTAN.

DRUG INTERACTIONS: If CEFOTAN and an aminoglycoside are used concomitantly, renal function should be carefully monitored, especially if higher dosages of the aminoglycoside are to be administered or if therapy is prolonged, because of the potential nephrotoxicity and ototoxicity of aminoglycoside antibiotics. Although, to date, nephrotoxicity has not been noted when CEFOTAN was given alone, it is possible that nephrotoxicity may be potentiated if CEFOTAN is used concomitantly with an aminoglycoside.

DRUG/LABORATORY TEST INTERACTIONS: A false positive reaction for glucose in urine may occur with Benedict's or Fehling's solution.

As with other cephalosporins, high concentrations of cefotetan may interfere with measurement of serum and urine creatinine levels of Jaffe reaction and produce false increases in the levels of creatinine reported.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY: Although long-term studies in animals have not been performed to evaluate carcinogenic potential, no mutagenic potential of cefotetan was found in standard laboratory tests.

Cefotetan has adverse effects on the testes of prepubertal rats. Subcutaneous administration of 500 mg/kg/day (approx 8-16 times the usual adult human dose) on days 6-35 of life (thought to be developmentally analogous to late childhood and prepuberty in humans) resulted in reduced testicular weight and seminiferous tubule degeneration in 10 of 10 animals. Affected cells included spermatogonia and spermatocytes; Sertoli and Leydig cells were unaffected. Incidence and severity of lesions were dose-dependent; at 120 mg/kg/day (approx 2-4 times the usual human dose), only 1 of 10 treated animals was affected, and the degree of degeneration was mild. Similar lesions have been observed in experiments of comparable design with other methylthiotetrazole-containing antibiotics and impaired fertility has been reported, particularly at high dose levels. No testicular effects were observed in 7-week-old rats treated with up to 1000 mg/kg/day SC for 5 weeks, or in infant dogs (3 weeks old) that received up to 300 mg/kg/day IV for 5 weeks. The relevance of these findings to humans is unknown.

USAGE IN PREGNANCY: Pregnancy Category B: Reproduction studies have been performed in rats and monkeys at doses up to 20 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to cefotetan. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

USAGE IN NURSING MOTHERS: Cefotetan is excreted in human milk in very low concentrations. Caution should be exercised when cefotetan is administered to a nursing woman.

PEDIATRIC USE: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

In clinical studies the following adverse effects were considered related to CEFOTAN therapy.

Gastrointestinal symptoms occurred in 1.5 percent of patients; the most frequent were diarrhea (1 in 80) and nausea (1 in 700).

Hematologic laboratory abnormalities occurred in 1.4 percent of patients and included eosinophilia (1 in 200), positive direct Coombs' test (1 in 250), and thrombocytosis (1 in 300).

Hepatic enzyme elevations occurred in 1.2 percent of patients and included a rise in SGPT (1 in 150), SGOT (1 in 300), alkaline phosphatase (1 in 700), and LDH (1 in 700).

Hypersensitivity reactions were reported in 1.2 percent of patients and included rash (1 in 150) and itching (1 in 700).

Local effects were reported in less than one percent of patients and included phlebitis at the site of injection (1 in 300), and discomfort (1 in 500).

DOSAGE AND ADMINISTRATION

TREATMENT: The usual adult dosage is 1 or 2 grams of CEFOTAN administered intravenously or intramuscularly every 12 hours for 5 to 10 days. Proper dosage and route of administration should be determined by the condition of the patient, severity of the infection, and susceptibility of the causative organism.

GENERAL GUIDELINES FOR DOSAGE OF CEFOTAN

Type of Infection	Daily Dose	Frequency and Route
Urinary Tract	1-4 grams	500 mg every 12 hours IV or IM 1 or 2 g every 24 hours IV or IM 1 or 2 g every 12 hours IV or IM
Other Sites	2-4 grams	1 or 2 g every 12 hours IV or IM
Severe	4 grams	2 g every 12 hours IV
Life-Threatening	6[*] grams	3 g every 12 hours IV

[*] Maximum daily dosage should not exceed 6 grams.

PROPHYLAXIS: To prevent postoperative infection in clean contaminated or potentially contaminated surgery in adults, the recommended dosage is 1 or 2 g of CEFOTAN administered once, intravenously, 30 to 60 minutes prior to surgery. In patients undergoing cesarean section, the dose should be administered as soon as the umbilical cord is clamped.

IMPAIRED RENAL FUNCTION: When renal function is impaired, a reduced dosage schedule must be employed. The following dosage guidelines may be used.

DOSAGE GUIDELINES FOR PATIENTS WITH IMPAIRED RENAL FUNCTION

Creatinine Clearance mL/min	Dose	Frequency
>30	Usual Recommended Dose[*]	Every 12 hours
10-30	Usual Recommended Dose[*]	Every 24 hours
<10	Usual Recommended Dose[*]	Every 48 hours

[*] Dose determined by the type and severity of infection, and susceptibility of the causative organism.

Cefotetan is dialyzable and it is recommended that for patients undergoing intermittent hemodialysis, one-quarter of the usual recommended dose be given every 24 hours on days between dialysis and one-half the usual recommended dose on the day of dialysis.

HOW SUPPLIED

CEFOTAN is a dry, white to pale yellow powder supplied in vials containing cefotetan disodium equivalent to 1 g and 2 g cefotetan activity for intravenous and intramuscular administration. The 1 g dose is available in 10 mL and 100 mL vials, and the 2 g dose is available in 20 mL and 100 mL vials. The vials should not be stored at temperatures above 22°C and should be protected from light.

1 g in 10 mL vial (NDC 0038-0376-10)
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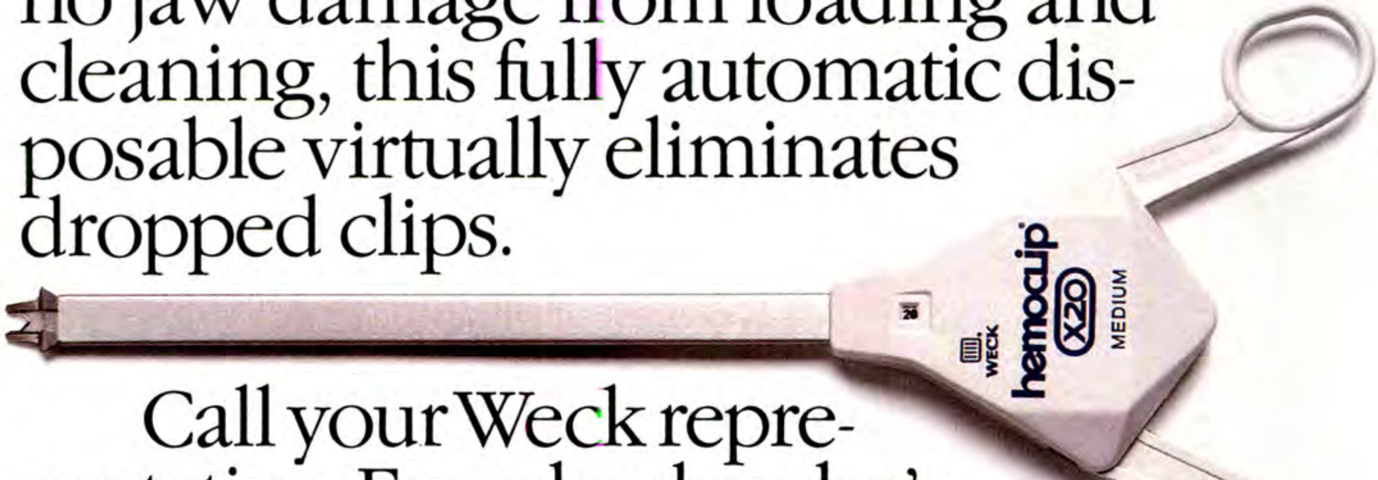

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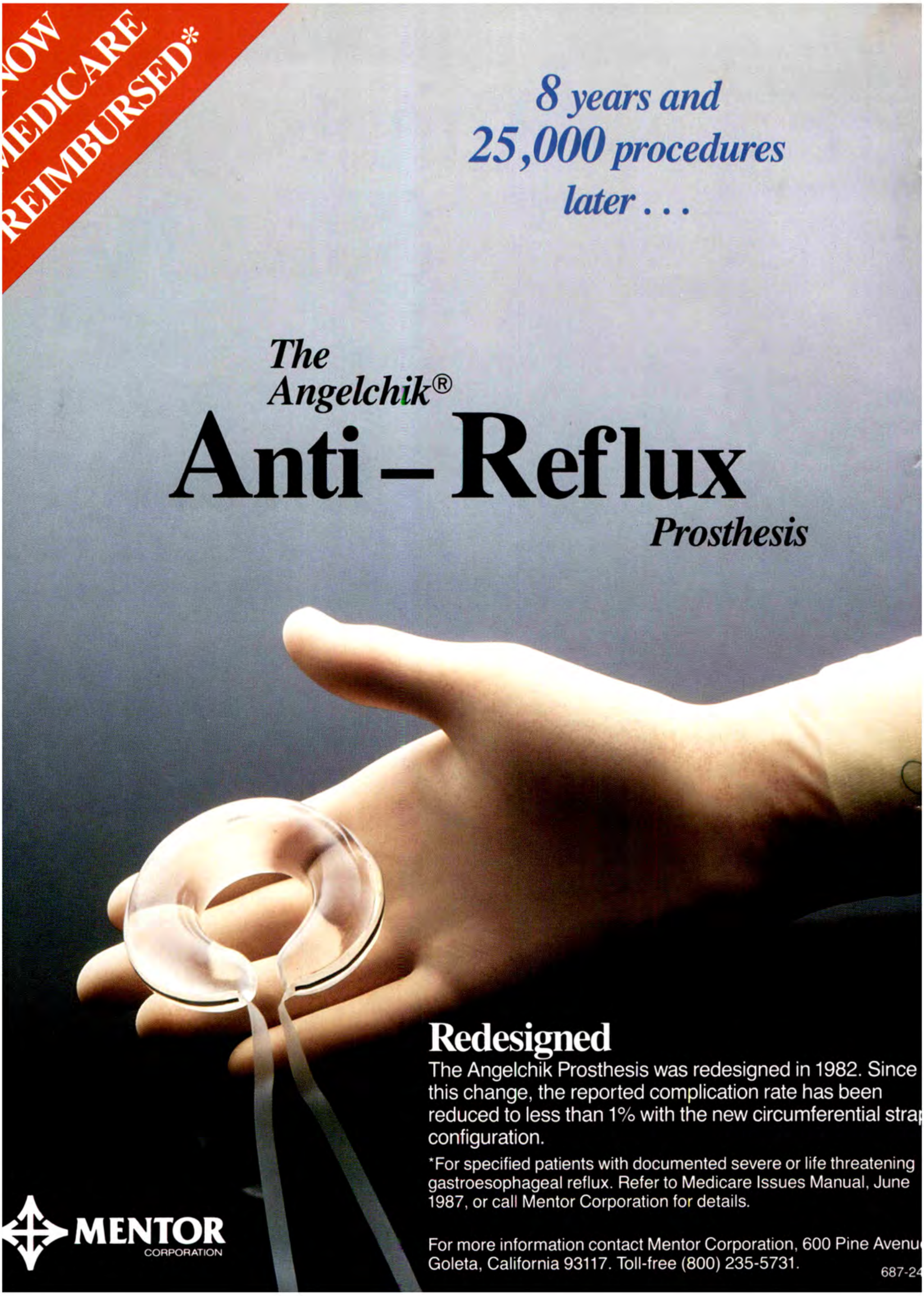NOW MEDICARE REIMBURSED*

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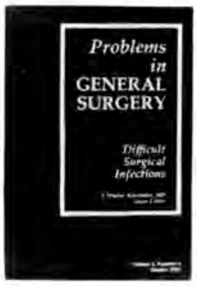

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Thrombostat must not be injected! Apply on the surface of bleeding tissue as a solution or powder.

INDICATIONS AND USAGE
Thrombostat (Thrombin, USP) is indicated as an aid in hemostasis wherever oozing blood from capillaries and small venules is accessible.

In various types of surgery, solutions of Thrombostat may be used in conjunction with Absorbable Gelatin Sponge, USP for hemostasis.

CONTRAINDICATIONS
Thrombostat is contraindicated in persons known to be sensitive to any of its components and/or to material of bovine origin.

WARNING
Because of its action in the clotting mechanism, Thrombostat must not be injected or otherwise allowed to enter large blood vessels. Extensive intravascular clotting and even death may result. Thrombostat is an antigenic substance and has caused sensitivity and allergic reactions when injected into animals.

PRECAUTIONS
General:
Consult the absorbable gelatin sponge product labeling for complete information for use prior to utilizing the thrombin-saturated sponge procedure.

Pregnancy—
Teratogenic effects: Pregnancy Category C. Animal reproduction studies have not been conducted with Thrombin, Topical (Bovine). It is also not known whether Thrombin, Topical (Bovine) can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Thrombin, Topical (Bovine) should be given to a pregnant woman only if clearly indicated.

Pediatric Use:
Safety and effectiveness in children have not been established.

ADVERSE REACTIONS
Allergic reactions may be encountered in persons known to be sensitive to bovine materials.

DOSAGE AND ADMINISTRATION
General: Solutions of Thrombostat may be prepared in sterile distilled water or isotonic saline. The intended use determines the strength of the solution to prepare. For general use in plastic surgery, dental extractions, skin grafting, neurosurgery, etc., solutions containing approximately 100 units per mL are frequently used. For this, 10 mL of diluent added to the 1000 unit package is suitable. Where bleeding is profuse, as from cut surfaces of liver and spleen, concentrations as high as 1000 to 2000 units per mL may be required. For this the 5000 unit vial dissolved in 5 mL or 2.5 mL, respectively, of the diluent supplied in the package is convenient. Intermediate strengths to suit the needs of the case may be prepared by selecting the proper strength package and dissolving the contents in an appropriate voulme of diluent. In many situations, it may be advantageous to use Thrombostat in dry form on oozing surfaces.

Caution: Solutions should be used immediately upon reconstitution. If necessary, refrigerate the solution and use within 3 hours of reconstitution.

The following techniques are suggested for the topical application of Thrombostat.
1. The recipient surface should be sponged (not wiped) free of blood before Thrombostat is applied.
2. A spray may be used or the surface may be flooded using a sterile syringe and small gauge needle. The most effective hemostasis results when the Thrombostat mixes freely with the blood as soon as it reaches the surface.
3. In instances where Thrombostat in dry form is needed, the vial is opened by removing the metal ring by flipping up the plastic cap and tearing counterclockwise. The rubber-diaphragm cap may be easily removed and the dried Thrombostat is then broken up into a powder by means of a sterile glass rod or other suitable sterile instrument.
4. Sponging of treated surfaces should be avoided in order that the clot remain securely in place.

Thrombostat may be used in conjunction with Absorbable Gelatin Sponge, USP as follows:
1. Prepare Thrombostat solution of the desired strength.
2. Immerse sponge strips of the desired size in the Thrombostat solution. Knead the sponge strips vigorously with moistened gloved fingers to remove trapped air, thereby facilitating saturation of the sponge.
3. Apply saturated sponge to bleeding area. Hold in place for 10 to 15 seconds with a pledget of cotton or a small gauze sponge.

Sterile Packages
Thrombostat Sterile Packages are available in two strengths, 5000 units and 10,000 units. A Sterile Package contains one sterile vial of Thrombostat, one sterile vial of Isotonic Saline Diluent, and one sterile transfer device. The Sterile Package may be used as follows:
1. Remove the Tyvek® blister lid by pulling up at the indicated corner. The sterile inner tray can be lifted out or introduced into the operating field.
2. The cover to the sterile inner tray is removed by pulling up on the finger tab, exposing the sterile contents.
3. Thrombostat solution of the desired strength is prepared using the transfer device.
4. Alternatively, when Thrombostat in dry form is needed, the vial is opened as described above and the dried Thrombostat broken up into a powder by means of a sterile glass rod or other suitable sterile instrument.

Thrombostat Kit
Thrombostat Kit contains one sterile 20,000 unit vial of Thrombostat, one sterile vial of Isotonic Saline Diluent, and one sterile pump sprayer cap. The kit may be used as follows:
1. Remove the Tyvek® blister lid by pulling up at the indicated corner. The sterile inner tray can be lifted out or introduced into the operating field.
2. The cover to the sterile inner tray is removed by pulling up on the finger tab, exposing the sterile contents.
3. Thrombostat solution of the desired strength is prepared and the pump sprayer cap inserted and seated on the Thrombostat solution vial. Note: Several strokes of the pump sprayer will be required before the Thrombostat solution is expelled.
4. Alternatively, when Thrombostat in dry form is needed, the vial is opened as described above and the dried Thrombostat broken up into a powder by means of a sterile glass rod or other suitable sterile instrument.

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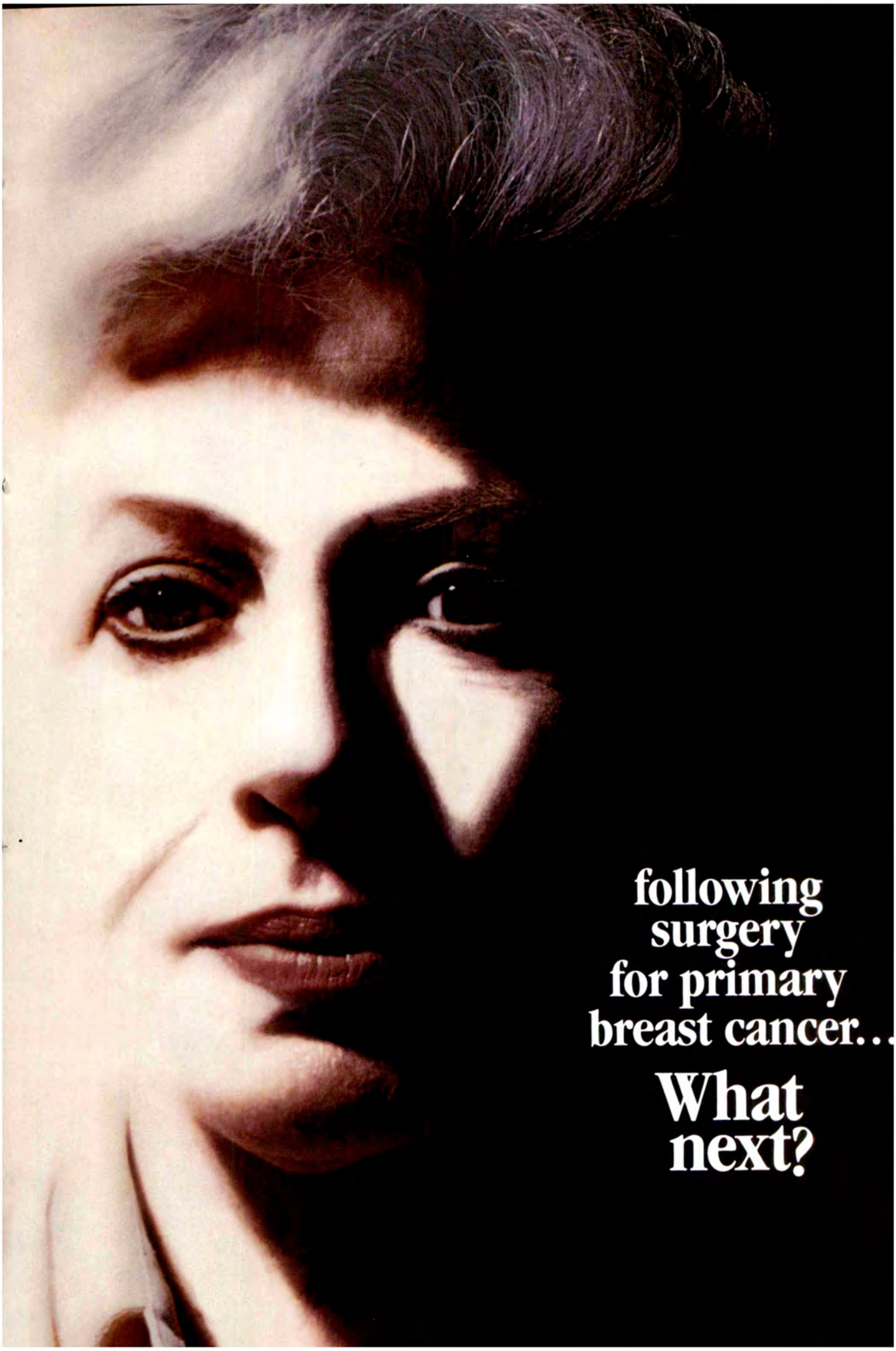
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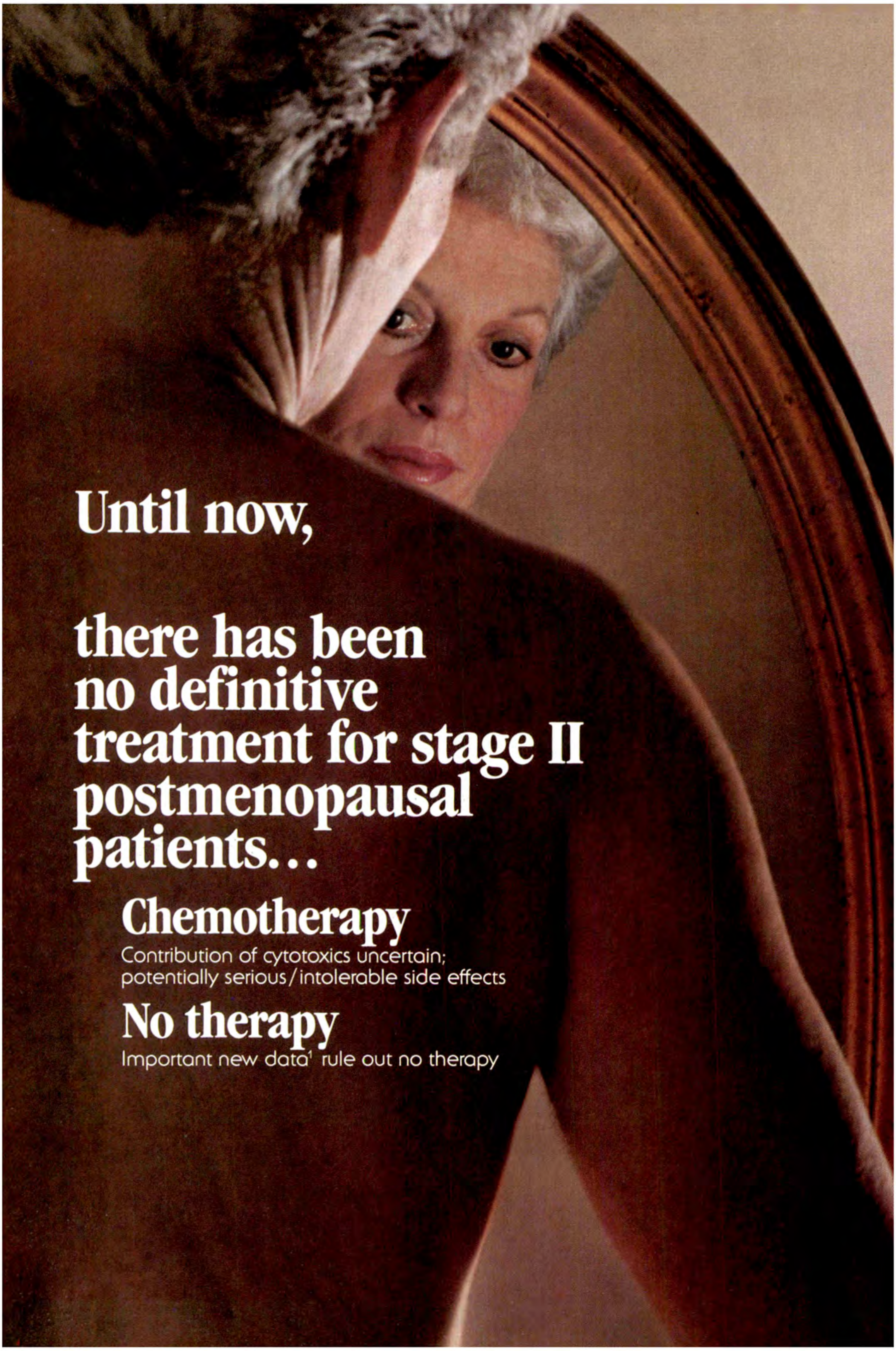

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there has been no definitive treatment for stage II postmenopausal patients. . .

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No therapy

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A recent National Institutes of Health consensus report states that following surgery, "Tamoxifen [NOLVADEX] should now be regarded as standard therapy for postmenopausal patients with positive axillary lymph nodes and positive hormone receptor status."[1]

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Please see next page for brief summary of prescribing information.

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Nolvadex® 10 MG TABLETS
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BRIEF SUMMARY
INDICATIONS AND USAGE: NOLVADEX is effective in the treatment of metastatic breast cancer in postmenopausal women. Available evidence indicates that patients whose tumors are estrogen receptor positive are more likely to benefit from NOLVADEX therapy.

NOLVADEX is effective in delaying recurrence following total mastectomy and axillary dissection in postmenopausal women with breast cancer (T1-3, N1, M0). The estrogen and progesterone receptor values may help to predict whether NOLVADEX therapy is likely to be beneficial. In some NOLVADEX adjuvant studies, most of the benefit to date has been in the subgroup with 4 or more positive axillary nodes.

CONTRAINDICATIONS: None known.

WARNINGS: Pregnancy Category D: NOLVADEX may cause fetal harm when administered to a pregnant woman. Individuals should not become pregnant while taking NOLVADEX. Effects on reproductive functions are expected from the antiestrogenic properties of the drug. In reproductive studies in rats at dose levels equal to or below the human dose, nonteratogenic developmental skeletal changes were seen and were found to be reversible. In addition, in fertility studies in rats and in teratology studies in rabbits using doses at or below those used in humans, a lower incidence of embryo implantation and a higher incidence of fetal death or retarded in utero growth were observed, with slower learning behavior in some rat pups. The impairment of learning behavior did not achieve statistical significance in one study, and, in another study where significance was reported, this was by comparing dosed animals with controls of another study. Several pregnant marmosets were dosed during organogenesis or in the last half of pregnancy. No deformations were seen and although the dose was high enough to terminate pregnancy in some animals, those that did maintain pregnancy showed no evidence of teratogenic malformations. There are no adequate and well-controlled studies in pregnant women. There have been reports of spontaneous abortions, birth defects, fetal deaths, and vaginal bleeding. If this drug is used during pregnancy or the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

Ocular changes have been reported in a few patients who, as part of a clinical trial, were treated for periods greater than one year with NOLVADEX at doses at least four times the highest recommended daily dose of 40 mg. The ocular changes consist of retinopathy and, in some patients, there are also corneal changes and a decrease in visual acuity.

In addition, a few cases of ocular changes including visual disturbance, corneal changes, and/or retinopathy have been reported in patients treated with NOLVADEX at recommended doses. It is uncertain if these effects are due to NOLVADEX.

As with other additive hormonal therapy (estrogens and androgens), hypercalcemia has been reported in some breast cancer patients with bone metastases within a few weeks of starting treatment with NOLVADEX. If hypercalcemia does occur, appropriate measures should be taken and, if severe, NOLVADEX should be discontinued.

PRECAUTIONS: General: NOLVADEX should be used cautiously in patients with existing leukopenia or thrombocytopenia. Observations of leukopenia and thrombocytopenia occasionally have been made, but it is uncertain if these effects are due to NOLVADEX therapy. Transient decreases in platelet counts, usually to 50,000-100,000/cu mm, infrequently lower, have been occasionally reported in patients taking NOLVADEX for breast cancer. No hemorrhagic tendency has been recorded and the platelet counts returned to normal levels even though treatment with NOLVADEX continued.

Laboratory Tests: Periodic complete blood counts, including platelet counts, may be appropriate.

Carcinogenesis: While no conventional bioassay has been conducted, endocrine changes in immature and mature mice were investigated in a 13-month study. Granulosa cell ovarian tumors and interstitial cell testicular tumors were found in mice receiving NOLVADEX, but not in the controls.

Mutagenesis: No genotoxic potential has been found in a battery of in vivo and in vitro tests with pro- and eukaryotic test systems with drug metabolizing systems present.

Impairment of Fertility: Fertility in female rats was decreased following administration of 0.04 mg/kg for 2 weeks prior to mating through day 7 of pregnancy. There was a decreased number of implantations, and all fetuses were found dead.

Following administration to rats of 0.16 mg/kg from days 7-17 of pregnancy, there were increased numbers of fetal deaths. Administration of 0.125 mg/kg to rabbits during days 6-18 of pregnancy resulted in abortion or premature delivery. Fetal deaths occurred at higher doses. There were no teratogenic changes in either rat or rabbit segment II studies. Several pregnant marmosets were dosed with 10 mg/kg/day either during organogenesis or in the last half of pregnancy. No deformations were seen, and, although the dose was high enough to terminate pregnancy in some animals, those that did maintain pregnancy showed no evidence of teratogenic malformations. Rats given 0.16 mg/kg from day 17 of pregnancy to 1 day before weaning demonstrated increased numbers of dead pups at parturition. It was reported that some rat pups showed slower learning behavior, but this did not achieve statistical significance in one study, and in another study where significance was reported, this was by comparing dosed animals with controls of another study.

The recommended daily human dose of 20-40 mg corresponds to 0.4-0.8 mg/kg for an average 50 kg woman.

Pregnancy Category D: See WARNINGS.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from NOLVADEX, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

ADVERSE REACTIONS: The most frequent adverse reactions to NOLVADEX are hot flashes, nausea and vomiting. These may occur in up to one-fourth of patients, but are rarely severe enough to require discontinuation of treatment.

Less frequently reported adverse reactions are vaginal bleeding, vaginal discharge, menstrual irregularities and skin rash. Usually these have not been of sufficient severity to require dosage reduction or discontinuation of treatment.

Increased bone and tumor pain and, also, local disease flare have occurred, which are sometimes associated with a good tumor response. Patients with increased bone pain may require additional analgesics. Patients with soft tissue disease may have sudden increases in the size of preexisting lesions, sometimes associated with marked erythema within and surrounding the lesions and/or the development of new lesions. When they occur, the bone pain or disease flare are seen shortly after starting NOLVADEX and generally subside rapidly.

Other adverse reactions which are seen infrequently are hypercalcemia, peripheral edema, distaste for food, pruritus vulvae, depression, dizziness, light-headedness and headache. There have been infrequent reports of thromboembolic events occurring during NOLVADEX therapy. Since for cancer patients in general an increased incidence of thromboembolic events is known to occur, a causal relationship to NOLVADEX remains conjectural. An increased incidence has been reported when cytotoxins are combined with NOLVADEX.

If adverse reactions are severe, it is sometimes possible to control them by a simple reduction of dosage without loss of control of the disease.

OVERDOSAGE: Acute overdosage in humans has not been reported. Signs observed at the highest doses following studies to determine LD_{50} in animals were respiratory difficulties and convulsions. No specific treatment for overdosage is known; treatment must be symptomatic.

DOSAGE AND ADMINISTRATION: One or two 10 mg tablets twice a day (morning and evening). In the three single agent adjuvant NOLVADEX studies noted above (See Clinical Pharmacology), NOLVADEX was administered for two years. The optimal duration of adjuvant therapy is not known.

HOW SUPPLIED: Tablets containing tamoxifen as the citrate in an amount equivalent to 10 mg of tamoxifen (round, biconvex, uncoated, white tablet identified with NOLVADEX 600 debossed on one side and a cameo debossed on the other side) are supplied in bottles of 60 tablets and 250 tablets. Protect from heat and light.

NDC 0310-0600 Rev J 2/87

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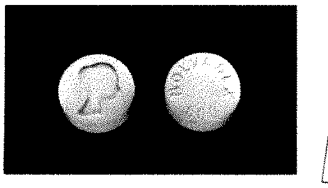

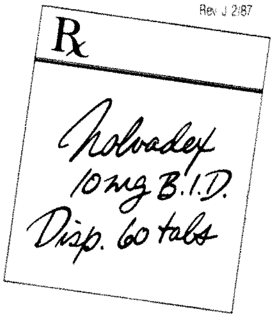

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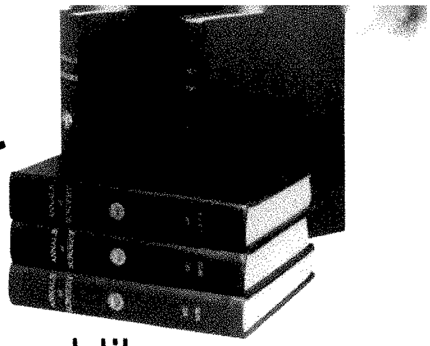

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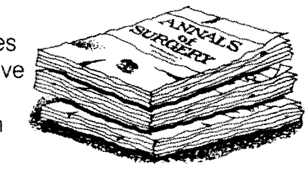

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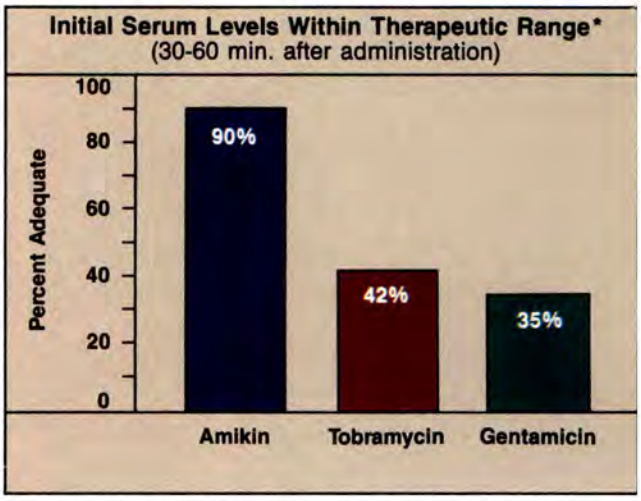

*Adapted from Holloway WJ: Management of sepsis in the elderly. *Am J Med* 80 (suppl 6B): 143-148, 1986.

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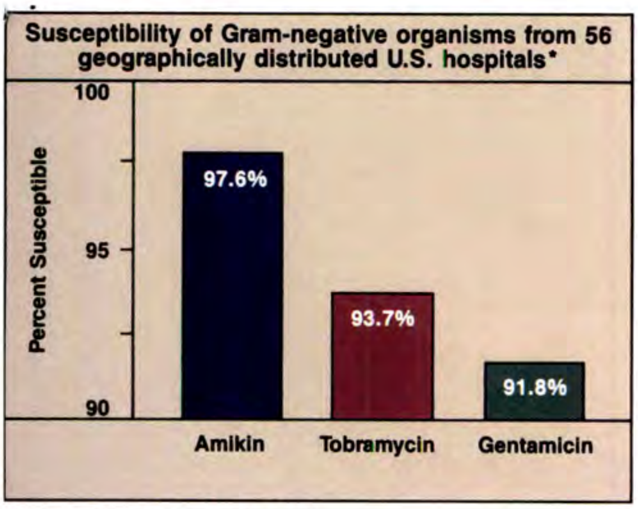
First-Dose Antimicrobial Activity.

Amikin has the broadest spectrum of any aminoglycoside.[2]



Total Amikin isolates = 247,503

In vitro data may not be directly correlated to clinical effectiveness. Data on file, Bristol Laboratories.

First-Dose Synergy.

In combination with antipseudomonal penicillins and latest generation cephalosporins, Amikin is overall the most synergistic of the aminoglycosides.[3,4]

First-Dose Economy.

The least expensive aminoglycoside is not necessarily the one with the lowest acquisition cost. It's the one *not* requiring replacement with a more effective agent.[5]

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BRIEF SUMMARY OF PRESCRIBING INFORMATION (1) 10/83
For complete prescribing information, please consult product literature.

WARNINGS

Patients treated with aminoglycosides should be under close clinical observation because of the potential ototoxicity and nephrotoxicity associated with their use.

Ototoxicity, both auditory and vestibular, can occur in patients treated at higher doses or for periods longer than those recommended. The risk of amikacin-induced ototoxicity is greater in patients with renal damage. High frequency deafness usually occurs first and can be detected only by audiometric testing. Vertigo may occur and may be evidence of vestibular injury.

The ototoxicity potential of amikacin in infants is not known. Until more safety reports become available, amikacin should be used in infants only in those specific circumstances when susceptibility testing indicates that other aminoglycosides cannot be used or are otherwise contraindicated, and when the infant can be observed closely for evidence of toxicity.

Aminoglycosides are potentially nephrotoxic. Renal and eighth-nerve function should be closely monitored in patients with known or suspected renal impairment and also in those whose renal function is initially normal but who develop signs of renal dysfunction during therapy. Such impairment may be characterized by decreased creatinine clearance, the presence of cells or casts, oliguria, proteinuria, decreased urine specific gravity or evidence of increasing nitrogen retention (increasing BUN or creatinine).

Evidence of impairment in renal, vestibular or auditory function requires discontinuation of the drug or dosage adjustment.

Serum concentrations should be monitored when feasible, and prolonged peak concentrations above 35 mcg/ml should be avoided. Urine should be examined for increased excretion of protein, the presence of cells and casts, and decreased specific gravity.

Concurrent and/or sequential use of topically or systemically neurotoxic or nephrotoxic antibiotics, particularly kanamycin, gentamicin, tobramycin, neomycin, streptomycin, cephaloridine, paromomycin, viomycin, polymyxin B, colistin and vancomycin should be avoided.

AMIKIN should not be given concurrently with potent diuretics (ethacrynic acid, furosemide, meralluride sodium, sodium mercaptomerin or mannitol). Some diuretics themselves cause ototoxicity, and intravenously administered diuretics enhance aminoglycoside toxicity by altering antibiotic concentrations in serum and tissue.

CONTRAINDICATIONS

A history of hypersensitivity to amikacin is a contraindication for its use.

WARNINGS

See "Warning" box above.

PRECAUTIONS

AMIKIN is potentially nephrotoxic, ototoxic, and neurotoxic. The concurrent or serial use of other ototoxic or nephrotoxic agents should be avoided either systemically or topically because of the potential for additive effects. Such agents include antibacterial drugs such as kanamycin, gentamicin, tobramycin, neomycin, streptomycin, cephaloridine, paromomycin, viomycin, polymyxin B, colistin and vancomycin as well as certain diuretic agents such as ethacrynic acid or furosemide.

Ototoxicity — See "Warning" box.

Nephrotoxicity — Since AMIKIN is present in high concentrations in the renal excretory system, patients should be well hydrated to minimize chemical irritation of the renal tubules. Kidney function should be assessed by the usual methods prior to starting therapy and daily during the course of treatment.

If signs of renal irritation appear (casts, white or red cells or albumin), hydration should be increased. A reduction in dosage (see "Dosage and Administration") may be desirable if other evidence of renal dysfunction occurs such as decreased creatinine clearance, decreased urine specific gravity, increased BUN, creatinine or oliguria. If azotemia increases or if a progressive decrease in urinary output occurs, treatment should be stopped.

Note: When patients are well hydrated and kidney function is normal the risk of nephrotoxic reactions with amikacin is low if the dosage recommendations (see "Dosage and Administration") are not exceeded.

Neurotoxicity — Neuromuscular blockade and muscular paralysis have been demonstrated in the cat with high doses of amikacin (188 mg/Kg). The possibility of neuromuscular blockade and respiratory paralysis should be considered when amikacin is administered concomitantly with anesthetic or neuromuscular blocking drugs. If blockade occurs, calcium salts may reverse this phenomenon.

Other — Cross-allergenicity among aminoglycosides has been demonstrated. As with other antibiotics the use of amikacin may result in overgrowth of nonsusceptible organisms. If this occurs, appropriate therapy should be instituted.

Pregnancy — Reproduction studies have been performed in rats and mice and have revealed no evidence of impaired fertility or harm to the fetus due to amikacin. There are no well-controlled studies in pregnant women but investigational experience does not include any positive evidence of adverse effects on the fetus. Although there is no clearly defined risk, such experience cannot exclude the possibility of infrequent or subtle damage to the fetus. AMIKIN should be used in pregnant women only when clearly needed.

It is not known whether this drug is excreted in human milk. As a general rule, nursing should not be undertaken while a patient is on a drug since many drugs are excreted in human milk.

ADVERSE REACTIONS

Ototoxicity — See "Warning" box.

Nephrotoxicity — Albuminuria, presence of red and white cells, casts, azotemia and oliguria have been reported.

Other — In addition to those described above, other adverse reactions which have been reported on rare occasions are skin rash, drug fever, headache, paresthesia, tremor, nausea and vomiting, eosinophilia, arthralgia, anemia, hypotension.

Overdosage — In the event of overdosage or toxic reaction, peritoneal dialysis or hemodialysis will aid in the removal of amikacin from the blood.

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A Prospective Randomized Trial of Regional *Versus* Systemic Continuous 5-Fluorodeoxyuridine Chemotherapy in the Treatment of Colorectal Liver Metastases

ALFRED E. CHANG, M.D., PHILIP D. SCHNEIDER, M.D., PH.D., PAUL H. SUGARBAKER, M.D., COLLEEN SIMPSON, R.N., MARY CULNANE, R.N., and SETH M. STEINBERG, PH.D.

From the Surgery Branch and Biostatistics and Data Management Section, National Cancer Institute, National Institutes of Health, Bethesda, Maryland

Sixty-four patients were entered into a randomized trial that evaluated intra-arterial (I.A.) *versus* intravenous (I.V.) 5-fluorodeoxyuridine (FUDR) for colorectal liver metastases. There was a significantly improved response rate for I.A. (62%) compared with I.V. (17%) treatment ($p < 0.003$). However, the improved response rate for patients in whom I.A. therapy was used did not translate to a significantly improved survival rate. The 2-year actuarial survival rates for the groups for which I.A. and I.V. therapy was used were 22% and 15% respectively, with the survival curves not differing significantly ($p = 0.27$). These results may have been due to the inclusion of patients with tumor in draining hepatic lymph nodes. The presence of tumor in hepatic lymph nodes was associated with a poorer prognosis. Analysis of a subgroup of patients with negative hepatic lymph nodes suggested an improved actuarial survival rate in patients for whom I.A. *versus* I.V. therapy was used ($p < 0.03$). The toxicity of I.A. FUDR was considerable, and side effects included chemical hepatitis (79%), biliary sclerosis (21%), peptic ulcers (17%), and gastritis/duodenitis (21%). The only major effect of toxicity of I.V. FUDR was severe diarrhea (59%). Regional I.A. FUDR allowed more drug delivery to liver tumors, which resulted in increased tumor responses when compared with use of systemic therapy. However, the small gain in survival seen in a select subgroup of patients with negative hepatic nodes appeared to be offset by the toxicity of I.A. FUDR.

REGIONAL CONTINUOUS INFUSION CHEMOTHERAPY *via* the hepatic artery for liver tumors has several theoretic advantages. Anatomic studies in a variety of animal species including humans have demonstrated that hepatic tumors derive most of their blood supply from the hepatic artery as opposed to the portal vein.[1,2] This phenomenon, along with the ability of the liver to metabolize certain chemotherapeutic drugs, allows a much higher local concentration of drug to reach the tumor with reduced systemic effects. Besides increasing local tumor concentrations of a chemotherapeutic agent, continuous infusion allows prolonged

---

Reprint requests and correspondence: Alfred E. Chang, M.D., Department of Surgery, The University of Michigan Medical Center, Ann Arbor, MI 48109.

Submitted for publication: June 15, 1987.

TABLE 1. *Patient Characteristics*

Characteristic*	IA Treatment (N = 32)	IV Treatment (N = 32)
Age (years)		
Median	57	61
Range	(37–77)	(37–70)
Sex		
Male/female	19/13	19/13
Primary tumor		
Dukes stage		
A, B	4	9
C	26	18
Unknown	2	5
Percentage hepatic replacement†		
<25	6	6
25–75	21	20
>75	5	6
Symptoms (yes/no)	11/21	9/23
Prior chemotherapy (yes/no)	5/27	6/26
CEA (ng/mL)		
Median	76	82
Range	(0–3840)	(4–3084)
LDH (U/L)		
Median	275	317
Range	(131–1200)	(159–2350)
Alkaline phosphatase (U/L)		
Median	193	183
Range	(66–581)	(43–1450)
Disease-free interval (months)‡		
Median	0	0
Range	(0–44)	(0–53)

* No significant differences between randomized groups.

† Assessed by computed tomography scan.

‡ Interval from primary colon resection to diagnosis of hepatic metastases.

IA = intra-arterial; IV = intravenous.

drug exposure to the tumor cells and thus potentially increases the cell-kill fraction.[3]

Extensive clinical experience with regional infusion chemotherapy of hepatic tumors has been reported since it was described in 1964.[4] Much of this experience has been with percutaneously placed hepatic artery catheters connected to extracorporeal pumps. These systems have been associated with mechanical and infectious complications.[5] An implantable pump that allows for continuous drug infusion was developed in 1972.[6] The first use of this device to deliver chemotherapeutic drugs to hepatic tumors was reported in 1980.[7] It has proven to be very reliable, without mechanical complications, and it is rarely subject to the problems seen with percutaneously placed catheters that are left in place for prolonged infusion.

Several Phase II studies have examined the use of this implantable pump to deliver 5-fluorodeoxyuridine (FUDR) in patients with colorectal hepatic metastases.[7-14] Response rates from 29 to 88% have been reported, with an overall survival rate from the time of pump implantation ranging from 8 to 18 months. The therapy can be associated with major toxicity. The monetary costs of this treatment and reported toxicity underscored the need for controlled studies to establish the impact of regional infusional chemotherapy on survival rate. This report describes a randomized prospective trial conducted by the Surgery Branch of the National Cancer Institute comparing the efficacy of regional *versus* systemic continuous FUDR chemotherapy *via* the implantable pump for patients with colorectal liver metastases.

Materials and Methods

Patients with isolated unresectable colorectal liver metastases were evaluated for study entry. To be eligible for entry, patients were to have no evidence of extrahepatic disease by radiologic assessment, a serum bilirubin level of less than 2 mg/dL, and a performance status of 0 or 1 (Eastern Cooperative Oncology Group Scale). Evaluation before operation included a history and physical examination, chest roentgenography, abdominal and chest computerized tomographic (CT) scans, a bone scan, a complete blood count, a chemistry profile, and carcinoembryonic antigen levels (CEA).

Sixty-four patients were randomized, 32 for regional intra-arterial (I.A.) infusion and 32 for systemic (I.V.) infusion. The protocol was closed to patient accrual on April 1, 1986, and all patient results were updated as of March 1, 1987. Median potential follow-up for all patients in the protocol is 23 months. Forty-nine of the 64 patients (76%) have died. Various patient characteristics are summarized in Table 1. There were no significant differences between the two groups regarding sex, age, stage of primary colon tumor, percentage hepatic replacement by tumor, symptoms, prior chemotherapy, CEA, lactic dehydrogenase, alkaline phosphatase, or disease-free interval.

Patients were randomized for their therapy after it was determined that their liver metastases were unresectable. Patients selected for I.A. therapy had a pump placed if there was no evidence of extrahepatic disease outside the regional draining hepatic (portal/celiac) nodes at the time of laparotomy. Previous reports had documented no benefit of I.A. FUDR therapy in the presence of extrahepatic disease.[12,14] The pump catheters were inserted as described by Neiderhuber et al.[15] A cholecystectomy was routinely performed to avoid chemically induced cholecystitis. When standard arterial anatomy was present, the catheter was inserted into the gastroduodenal artery and positioned at the junction to the common hepatic artery. Ligation of the distal gastroduodenal artery, right gastric artery, and any other

TABLE 2. *Tumor Responses with FUDR*

Response	IA Treatment	(%)	IV Treatment	(%)
Complete*	1	(62)	1	(17)
Partial†	12		4	
Stable/progression	8	(38)	24	(83)
Total	21		29	

* Complete resolution of tumor on CT scan with normalization of CEA.

† Greater than or equal to 50% reduction of evaluable tumor on CT scan.

FUDR = 5-fluorodeoxyuridine; IA = intra-arterial; IV = intravenous; CT = computed tomography; CEA = carcinoembryonic antigen.

branches supplying the stomach or duodenum arising from the common hepatic distal to the gastroduodenal take-off was performed. Total liver perfusion was confirmed during operation with injection of 3 mL of fluorescein dye visualized by a Woods lamp. After operation a ^{99}technetium-labeled macroaggregated albumin scan through the sideport of the pump was performed to confirm adequacy of liver perfusion and repeated during follow-up evaluations. Patients selected for I.V. FUDR therapy had catheters placed into the superior vena cava *via* the cephalic vein. A subcutaneous pocket was created in the infraclavicular region to place the pump.

Of the 32 patients selected at random for I.A. therapy 21 had pumps placed for treatment. Eleven were not treated because of patient refusal after randomization (two patients) or the presence of extrahepatic disease outside hepatic lymph nodes (nine patients). Of the 32 patients selected at random to receive I.V. treatment, 29 received therapy and three did not. The latter occurred because of a death after operation from liver failure (one patient) and development of extrahepatic disease (carcinomatosis) that precluded treatment (two patients).

FUDR was administered continuously for 14 days, alternating with 14 days of water and heparin (17,500 U/50 mL) in the pump. Patients received I.A. FUDR at a starting dose of 0.3 mg/kg/day. Chemistry profiles were obtained every 2 weeks to monitor for hepatic toxicity. Doses were held for any abnormal liver function tests (LFTs) above baseline. Subsequent doses were administered at reduced doses when toxicity resolved. Doses were reduced 25, 50, and 75% for mild (≤2× LFT), moderate (>2, ≤3× LFT; gastritis symptoms), or severe (>3× LFT; or peptic ulcer disease), respectively. All patients were maintained on cimitidine or ranitidine while receiving I.A. FUDR. Midway through the trial the starting dose was reduced to 0.2 mg/kg/day in attempts to avoid severe hepatic toxicity. This did not appear to impact on incidence of toxicity nor response rates.

I.V. FUDR was started at a dose of 0.125 mg/kg/day. Diarrhea was the major toxicity of I.V. FUDR. Doses were reduced 25, 50, and 75% for mild (≤6 loose stools/day), moderate (7–12 loose stools/day), or severe (>12 loose stools/day) diarrhea, respectively. No bone marrow suppression occurred with this dose regimen.

Patients were treated with three cycles of drug and were re-evaluated for response by CT scan. Chest roentgenographs were performed every 3 months, and chest CT scans every 6 months. A complete response was indicated by disappearance of all disease by CT scan and normalization of CEA levels. A partial response was defined by greater than or equal to 50% reduction in the sum of the products of the perpendicular diameters of all sentinel lesions identified by CT scan. Progressive disease was defined as a greater than 25% increase in the size of evaluable tumor or the presence of any new lesion in the liver or at extrahepatic sites. Patients were treated for another three cycles if tumor responded or remained stable and were re-evaluated for response. FUDR was discontinued for patients who progressed. Once a patient progressed, there was no cross-over to the other arm of the study.

Survival from the time of randomization was the primary endpoint of the study. Estimates of the survival curves were computed by use of the method of Kaplan and Meier.[16] The test of Mantel and Haenzel was used for comparison of survival rates in the two treatment arms.[17] In comparing proportions in two groups, we have used the Fisher exact test.[18] All p values are two tailed.

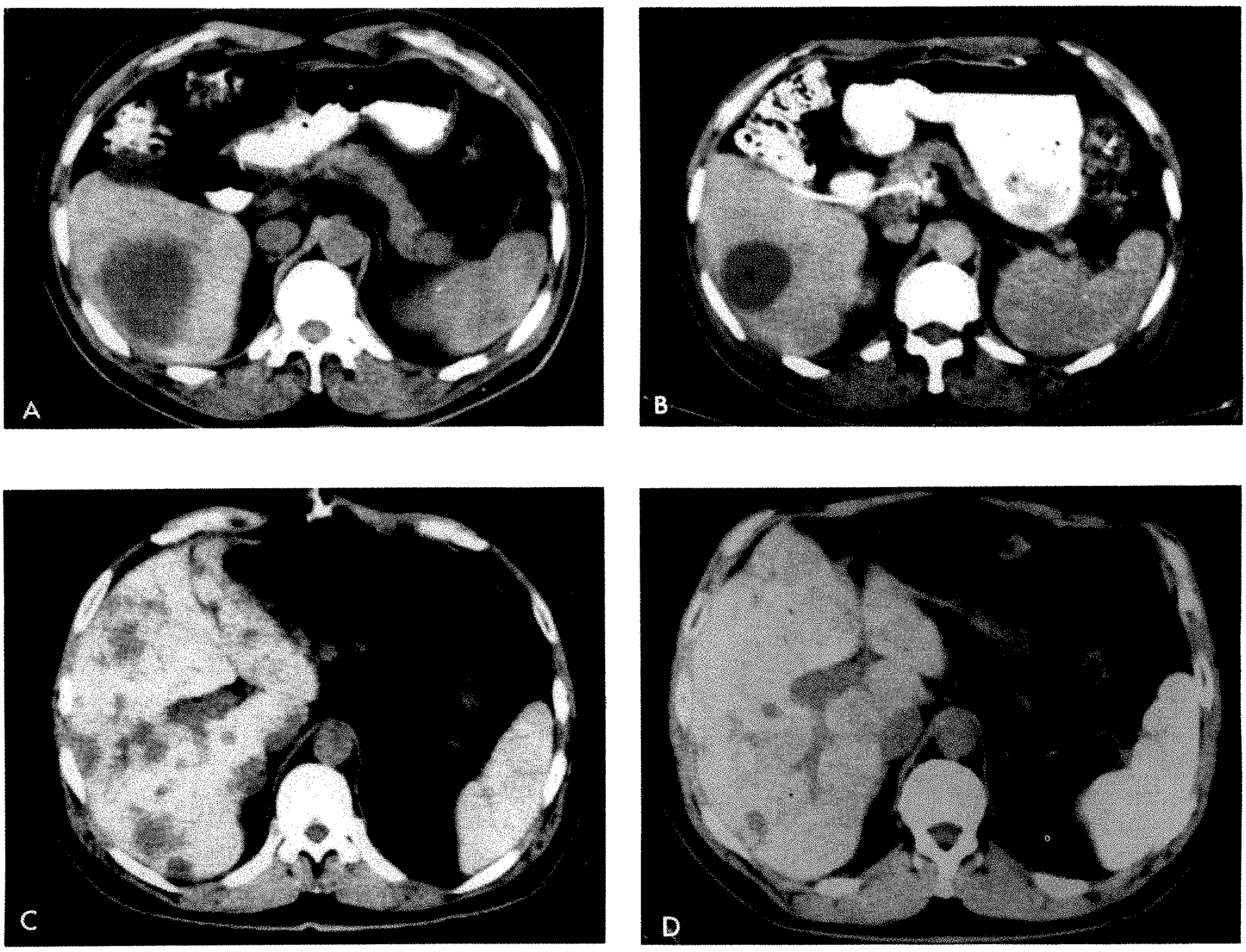
Results

Response Rates

The response rates for all randomized treated patients are indicated in Table 2. The overall response rate (complete and partial) for I.A. therapy was 13 of 21 patients (62%) and was significantly better than the rate of five of 29 patients (17%) seen for I.V. therapy ($p < 0.003$). There were two complete responses, one in each randomized group. Figure 1 illustrates the nature of the responses that were seen in two patients who had I.A. therapy.

The duration of response and sites of first failure are indicated in Table 3. The median duration of response was 7 and 9 months for I.A. and I.V. therapy, respectively. Of the 13 patients responding to I.A. therapy, six had their site of first relapse in extrahepatic sites compared with one of five in the I.V. treatment responders.

CEA levels were monitored every 2 weeks in all patients. Figure 2 is a graph of the percentage change in median CEA compared with pretreatment levels in patients who had I.A. and I.V. treatment and had elevated



FIGS. 1A–D. Responses documented by CT scan. *A*. Patient 10 had multiple liver metastases with a large tumor noted in the right lobe before therapy and a CEA level of 47 ng/mL. *B*. The same patient demonstrated a significant response in all tumors by CT scan with a decrease in CEA level to less than 2 ng/mL after receiving three cycles of I.A. FUDR therapy. *C*. Another patient (Patient 12) had bilobar metastases documented by CT scan and a CEA level of 37 ng/mL. *D*. After three cycles of I.A. FUDR, Patient 12 had a dramatic response in all liver lesions with a decrease in CEA level to less than 5 ng/mL. Both patients subsequently had relapses (see Table 3).

pretreatment CEA determinations. Three patients with normal pretreatment CEA values of less than 5 ng/mL (1 IV, 2 IA) were not included in the plot because CEA values were not reflections of their tumor burden. After the third cycle of chemotherapy, when patients were evaluated for response, the median percentage of pretreatment CEA levels was 28% and 168% for I.A. and I.V. treatment groups, respectively. Alternatively, after the third cycle, 12 of 20 patients who had I.A. therapy had their CEA levels decrease by more than 50% compared with 3 of 28 who had I.V. treatment ($p < 0.001$). CEA levels alone were not used to define a tumor response.

Survival

The survival of all randomized patients is depicted in Figure 3. The 2-year actuarial survival rates for the randomized I.A. and I.V. treatment groups were 22% and 15%, and the two curves were not significantly different from one another ($p = 0.27$). As was previously indicated, not all patients received treatment (see "Materials and Methods"). Patients found to have extrahepatic disease outside regional hepatic lymph nodes at the time of laparotomy for I.A. pump insertion did not have a pump placed. This would have allowed selection of a more favorable patient population in the I.A. treatment group because patients randomized for I.V. therapy were not required to have a laparotomy for staging purposes. Figure 4 depicts the survival of all randomized patients that received the assigned treatment. Patients who had I.A. and I.V. treatment had 2-year actuarial survival rates of 34% and 17%, respectively, with some evidence of difference between the curves ($p = 0.06$). This demonstrated a trend toward an improved survival rate in the selected group patients who had I.A. therapy.

The presence of tumor in hepatic lymph nodes did not exclude patients from receiving treatment. Biopsies were performed routinely on these nodes in patients randomized for I.A. therapy and also in patients who were chosen for I.V. therapy after an abdominal exploration revealed their liver metastases to be unresectable. The presence of positive hepatic lymph nodes appears to be a significant prognostic indicator (Fig. 5). For all treated patients who had I.A. therapy (including three pilot patients who satisfied the eligibility criteria), the median survival rate for patients with negative and positive hepatic nodes was 27 and 17 months, respectively, with the curves differing significantly (p = 0.024). Therefore, patients with negative hepatic nodes had improved survival rates compared with patients whose nodes were positive.

An analysis with patients who had I.A. and I.V. treatment was performed in randomized patients with negative hepatic nodes documented at laparotomy. As shown in Figure 6, patients who had I.A. treatment did significantly better than the group that had I.V. treatment (p = 0.03), with 2-year actuarial survival rates of 47% and 13%, respectively. A separate analysis that included the three pilot patients with I.A. treatment, all of whom had negative hepatic nodes, revealed a significant improved survival in patients who had I.A. treatment compared with I.V. therapy (data not shown).

Toxicity

Toxicity to I.A. therapy was significant. Table 4 lists the toxicity seen in all patients who had I.A. (including three pilot patients) and I.V. treatment. "Chemical" hepatitis, which was manifested as elevations in baseline liver function tests, was seen in 79% of patients with I.A. therapy compared with 7% of those with I.V. treatment. The usual changes seen were a transient elevation of liver functions seen 2 weeks after chemotherapy was started. These changes would often revert to baseline values after another 2–4 weeks. Minimal liver function abnormalities resulting from I.V. FUDR were seen. Eight of 24 patients who had I.A. treatment had elevations of total bilirubin greater than 3 mg/dL compared with none of 29 patients with I.V. therapy during some time interval of their treatment. Biliary sclerosis documented by percutaneous transhepatic cholangiograms was seen in five of 24 patients with I.A. treatment. All five patients had tumor responses (two complete, three partial) at the time the diagnosis of biliary sclerosis was made. One of these patients died of liver failure secondary to biliary cirrhosis with only two small metastatic nodules remaining in the liver.

Gastrointestinal toxicity was seen in both treatment groups but was manifested in different forms. In the group that had I.A. treatment, peptic ulcers developed

TABLE 3. *Sites of First Failure in Patients Who Responded*

Patient No.	Duration of Response (Months)	Sites of First Failure
IA treatment responders		
1	23	Liver
2	16	Liver
3	5	Liver/bowel/lung
4	3	Liver/retroperitoneum/lung
5	5	Lung
6	4	Lung
7	>17	*
8	1	Pelvis
9	>10	†
10	8	Liver
11	12	Retroperitoneum
12	12	Peritoneum
13	2	Lung, abdominal carcinomatosis
Median	7	
IV treatment responders		
14	10	Liver
15	10	Liver
16	7	Liver
17	9	Liver
18	>12	Pelvis, abdominal wall‡
Median	9	

* Complete response, remains disease-free.
† Disease stable after initial response.
‡ Complete response, recurred in pelvis and abdominal wall.
IA = intra-arterial; IV = intravenous.

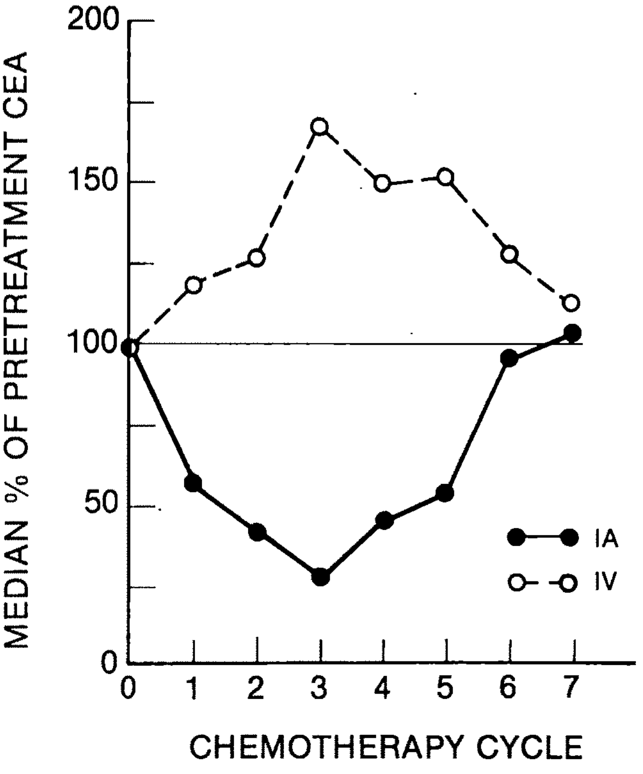


FIG. 2. Percentage change in median CEA levels compared with pretreatment levels in patients treated with I.A. *versus* I.V. therapy.

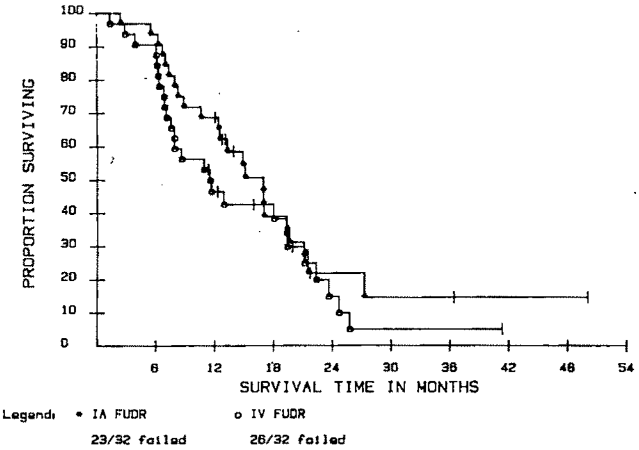


FIG. 3. Hepatic metastases infusion: survival of all randomized patients. The 2-year actuarial survival rates for randomized I.A. and I.V. groups were 22% and 15%, and the two curves were not significantly different (p = 0.27).

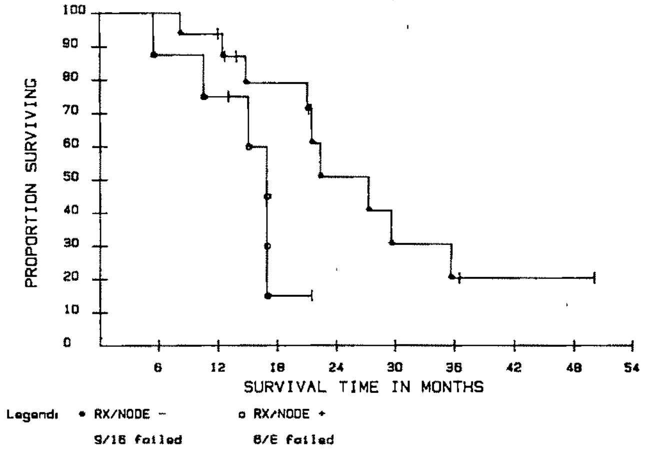


FIG. 5. Survival of all patients who had I.A. treatment with respect to hepatic node status. The median survival for patients with negative and positive hepatic nodes was 27 and 17 months, respectively, with the curves differing significantly (p = 0.024).

in the stomach or duodenum in four of 24 patients that were documented by upper gastrointestinal studies or endoscopic examination. One patient presented with a perforated ulcer requiring immediate operative intervention. Symptoms of gastritis and/or duodenitis were seen in five of the patients who had I.A. treatment. In the patients who had I.V. therapy there were no problems with peptic ulcers and minimal problems with gastritis. However, with I.V. therapy, 59% of patients complained of diarrhea that was severe enough to require six patients to be hospitalized for hydration.

The dose of FUDR given over repeated cycles in all treated patients is depicted in Figure 7. The dose of I.A. FUDR drug was significantly greater than systemic doses during the first five cycles of treatment. As can be seen, I.A. drug dose had to be decreased over successive courses. Dose modifications of I.A. therapy were mainly required because of hepatic toxicity and by the sixth cycle were not significantly different from I.V. doses. Dose modifications for I.V. therapy were less frequent, and the mean FUDR dose administered was relatively constant over time.

Discussion

This randomized, controlled trial has addressed the issue of whether regional continuous arterial perfusion FUDR therapy *via* the implantable pump offers any

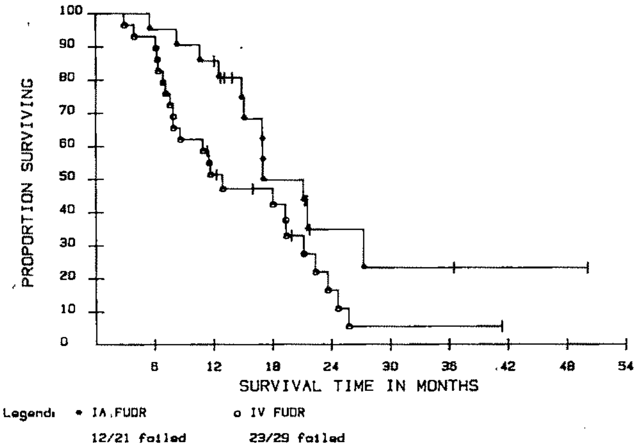


FIG. 4. Hepatic metastases infusion: survival of all randomized patients who received the assigned treatment. The 2-year actuarial survival rates for I.A. and I.V. treatment groups were 34% and 17%, respectively, with some evidence of difference between the curves (p = 0.06).

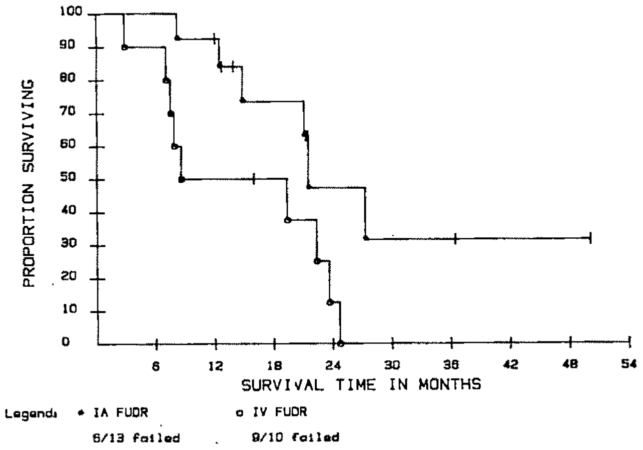


FIG. 6. Survival of patients with documented negative hepatic lymph nodes who were randomized for I.A. and I.V. treatment. The 2-year actuarial survival rates for I.A. and I.V. treatment groups were 47% and 13%, respectively, with the curves differing significantly (p = 0.03).

benefit in survival to patients with unresectable colorectal liver metastases. Previous reports for which FUDR was administered *via* the implantable pump have demonstrated significant tumor response rates in the range of 30–88% when various response criteria have been used.[7–14] We have confirmed that higher response rates are achieved when FUDR is administered intra-arterially *versus* intravenously at maximum tolerated doses. The response rates for the groups that had I.A. and I.V. treatment were 62% and 17%, respectively, which were significantly different. This most likely reflects the ability to deliver higher concentrations of the drug to the tumor regionally for several reasons. First, the hepatic extraction of FUDR is greater than 98% and allowed higher doses of I.A. drug to be administered without development of systemic toxicity.[19] Secondly, even at comparable doses, I.A. therapy should theoretically deliver higher doses of drug to the tumor because macroscopic hepatic tumors are mainly supplied by the hepatic artery. Also, inflow drug concentrations to the liver should be higher for arterial infusion *versus* systemic infusion when equal amounts of drug are administered because of the large blood volume dilution that occurs during systemic infusion. During the study, doses of I.A. drug were either greater than or equal to I.V. drug doses (see Fig. 7).

The most critical analysis is the impact of treatment on overall survival. After randomization, patients selected for I.A. treatment and who were found to have extrahepatic disease beyond hepatic lymph nodes did not have pumps placed. This was done because it was known that this potentially toxic treatment was not beneficial to patients with documented extrahepatic tumor.[12,14] These patients have been kept in the randomized group for analysis. Patients randomized for I.V. therapy were not required to have staging laparotomies and would have potentially occult extrahepatic tumor treated by systemic drug. With the use of this strategy, there was no difference in overall survival rate between patients randomized for I.A. or I.V. therapy with 2-year actuarial survival rates of 22% and 15%, respectively (Fig. 3). When one analyzes the survival data of patients who received treatment, excluding patients who did not, there was a trend in improved survival in the group with I.A. treatment compared with those who had I.V. treatment (Fig. 4). With more patients this may have resulted in an improved survival rate for the I.A. treatment group; however, this should be attributed to the selection of patients for I.A. treatment (*i.e.,* exclusion of patients with extrahepatic disease beyond hepatic lymph nodes).

An interesting observation was the effect of hepatic lymph node involvement on the survival of patients. Among all the patients who had I.A. treatment (21 selected at random and three pilot patients), hepatic lymph node involvement was not associated with response but was associated with survival. Those who had I.A. treatment and had negative hepatic lymph nodes (62% of the group) did significantly better than patients with positive hepatic lymph nodes (Fig. 5). Patients who had I.A. therapy and had positive hepatic nodes did not do significantly better than untreated patients excluded from therapy because of occult intra-abdominal extrahepatic disease (data not shown). This suggests that the presence of tumor in hepatic lymph nodes could have significant prognostic implications. Fortner et al. has also reported that a tumor in hepatic lymph nodes was associated with a poorer prognosis in a personal series of 109 evaluable patients receiving intrahepatic chemotherapy for colorectal liver metastases.[20] A tumor in these lymph nodes represents "remetastasis" from liver metastases.[21] Patients with involvement of hepatic nodes should not be considered for regional therapies because it appears to be a harbinger of systemic disease. This principle also applies to patients being considered for resection of colorectal liver metastases. Hughes et al.

TABLE 4. *Toxicities of FUDR Infusion*

Toxicity	IA Treatment (%) (N = 24)	IV Treatment (%) (N = 29)
Chemical hepatitis	19 (79)	2 (7)
Biliary sclerosis	5 (21)	0 (0)
Peptic ulcer	4 (17)	0 (0)
Gastritis/duodenitis	5 (21)	2 (7)
Diarrhea	3 (13)	17 (59)
Nausea/vomiting	5 (21)	10 (35)
Vascular thrombosis	5 (21)	2 (7)
Stomatitis	0 (0)	4 (14)

IA = intra-arterial; IV = intravenous.

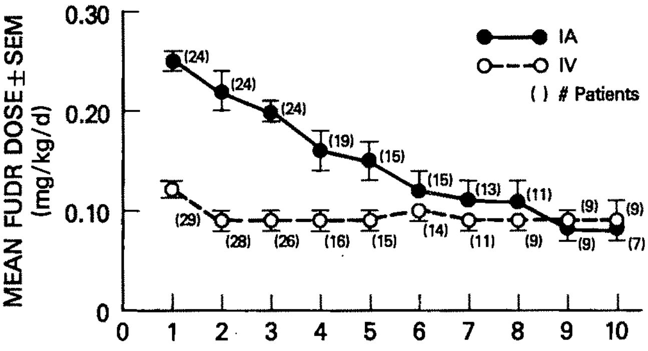


FIG. 7. Mean dose of I.A. or I.V. FUDR administered. I.A. drug dose was significantly greater than I.V. drug dose during the first five courses.

reported a collected review of 859 resections for colorectal liver metastases in which there were no long-term survivors in a group of patients documented to have involvement of hepatic nodes.[22]

In a subgroup analysis of patients whose hepatic lymph nodes were documented to be negative, a significant survival advantage to I.A. therapy was found (Fig. 6). Two-year actuarial survival rates in the I.A. and I.V. groups were 47% and 13%, respectively. However, this was a small group of patients, and the results need to be confirmed in a larger series. Even if patients are adequately staged and found to be appropriate for regional infusion therapy, the toxicity of therapy needs to be considered.

I.A. FUDR was associated with major toxicity. The most common effect of toxicity was to the hepatobiliary system, with chemical injury to normal hepatocytes and ductal structures. The hepatic toxicity was similar to that encountered by others.[3,4] Our incidence of biliary sclerosis was 21% and led to a treatment-related death resulting from liver failure. This entity was first described by Hohn et al.[23] This complication may be related to the specific drug, FUDR, because there have been no other reports of this complication with other drugs delivered through the hepatic artery. Other effects of toxicity associated with I.A. FUDR are gastrointestinal problems such as peptic ulcers and gastritis/duodenitis, seen in 38% of patients. This coincides with the incidence reported by Kemeny et al.[13] Histamine H_2 receptor antagonists did not prevent these problems because all patients were treated with these medications. Resolution of these side effects required FUDR dose reduction or cessation.

This is one of only a few prospective, randomized studies that have been reported or are being conducted to evaluate arterial infusion therapy for colorectal hepatic metastases.[25] The first report in 1979 by Grage et al. was a Central Oncology Group study evaluating I.A. *versus* I.V. 5-fluorouracil (5-FU).[26] Sixty-one evaluable patients were entered into that trial. Only one "induction" dose of I.A. 5-FU was administered, followed by weekly systemic 5-FU in patients randomized for I.A. therapy. This was a major drawback with the study because repeated courses of I.A. drug were not given. There were no differences in response or survival rates between the randomized groups in that study. Since the introduction of the implantable pump, catheter complications related to prolonged hepatic artery infusion have been greatly reduced. Several randomized, prospective studies have been initiated evaluating I.A. FUDR *versus* a control group receiving systemic therapy. Preliminary results of a study at Memorial Sloan-Kettering Cancer Center have been reported by Kemeny and Daly.[27] Fifty evaluable patients were randomized for I.A. *versus* I.V. FUDR therapy; patients who progressed were crossed-over to the other arm. For I.A. therapy, a 43% response rate was noted compared with 32% for I.V. treatment. Survival data will be difficult to interpret because patients were crossed-over to the other arm. Hohn et al. reported their preliminary results in a similarly designed study.[28] Patients were randomized for I.A. *versus* I.V. FUDR therapy, with a cross-over when patients progressed. In 110 evaluable patients, I.A. therapy was associated with a 37% major response rate that was significantly better than 10% for the I.V. treatment group. Survival data were not analyzed in that report. Other randomized trials have not been reported to date.

Our experience indicated that I.A. FUDR is associated with significantly improved response rates of colorectal liver metastases compared with continuous I.V. FUDR. However, in our randomized study there was no impact on overall survival rate. This may be a significant observation that relates to all locoregional approaches to cancer. Despite adequate control of disease in one site, the patient may manifest disease elsewhere. For recurrent colon cancer, isolated hepatic recurrences are seen only 6% of the time compared with 80% of recurrences that are in multiple sites.[29] The status of hepatic lymph nodes was a major prognostic factor and when involved by tumor should be a contraindication to regional chemotherapy to the liver. This was seen in approximately 40% of our patients. In a subgroup of patients with negative hepatic nodes, I.A. therapy appeared to improve survival compared with I.V. therapy. However, because of the major hepatobiliary and gastrointestinal toxicity associated with I.A. FUDR therapy the improved survival advantage was not worthwhile in the best selected patient population. Another drawback was the morbidity experienced by patients who were explored and could not be treated because of extrahepatic disease.

Survival is certainly the most critical endpoint in evaluating new treatments. However, palliation of the patient and impact on their quality of life should also be considered. Even if survival is not prolonged, the high response rates associated with regional chemotherapy may potentially be an effective palliative approach to patients with unresectable colorectal liver metastases. Patt et al. reported an improved performance status in patients who respond to I.A. chemotherapy.[30] Future studies should define the impact of I.A. therapy on palliation and quality of life. This underscores the need to find treatments that are not associated with significant toxicities. Our present efforts are involved in a Phase I study of a different chemotherapeutic agent, iododeoxyuridine (IUdR), given by continuous I.A. administration to patients with colorectal liver metastases. This is a tumoricidal drug with radiosensitization properties that can be combined with radiation therapy.[31]

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Adjuvant Postoperative Radiation Therapy for Colonic Carcinoma

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One hundred thirty-three patients with Stage B2, B3, and C colonic carcinoma had resection for curative intent followed by adjuvant postoperative radiotherapy to the tumor bed. The 5-year actuarial local control and disease-free survival rates for these 133 patients were 82% and 61%, respectively. Stage for stage, the development of local regional failure was reduced for patients receiving postoperative radiotherapy compared with a historic control series. Local recurrence occurred in 8%, 21%, and 31% of patients with Stage B3, C2, and C3 tumors who had radiation therapy, respectively, whereas the local failure rates were 31%, 36%, and 53% in patients treated with surgery alone. There was a 13% and 12% improvement in the 5-year disease-free survival rate in the patients with Stage B3 and C3 lesions who had radiotherapy compared with the historic controls. For patients with Stage C disease, local control and disease-free survival rates decreased progressively with increasing nodal involvement; however, local control and disease-free survival rates were higher in the patients who had radiotherapy than in those who had surgery alone. Failure patterns in the patients who had radiotherapy did not show any notable changes compared with those for patients who had surgery alone. Postoperative radiation therapy for Stage B3, C2, and C3 colonic carcinoma is a promising treatment approach that deserves further investigation.

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RECENT REPORTS have described the failure patterns and identified patients at high risk for recurrence after attempted curative resection of colonic (nonrectal) carcinoma.[1-4] Subsets of patients at risk for local-regional failure include all patients with tumors extending through the bowel wall with adherence or invasion of adjoining structures or lymph node involvement with extension through the bowel wall.

Since 1976, patients with advanced stage colonic carcinoma have been offered treatment with postoperative radiation therapy to the tumor bed at the Massachusetts General Hospital. Duttenhaver et al. have described the indications and technical details of treatment and have analyzed local control and survival of the first 80 patients treated with relatively short follow-up.[5] This analysis indicated that postoperative irradiation to doses of 5000 cGy or greater improved local control and perhaps survival. The objective of this report is to assess long-term follow-up and failure patterns of patients treated with adjuvant postoperative radiation therapy.

Materials and Methods

From April 1976 to August 1985, 133 patients had resection with curative intent of a primary colonic neoplasm followed by postoperative radiation therapy in the Department of Radiation Medicine at the Massachusetts General Hospital. A colonic tumor was defined as one that arose from the large bowel above the peritoneal reflection without extension into the rectum. All patients were evaluated for at least 1 year after surgery, with mean and median follow-up periods of 44 months and 39 months, respectively, with a range of 12–110 months. Of the 133 patients, 60 were men and 73 were women. The mean age at surgery was 67.5 years, with a range of 21–85 years.

Primary lesions were described in terms of stage and of location in the bowel wall. In addition, the presence or absence of complete obstruction or perforation at the primary site was noted.[4] Pathologic staging was based on the Gunderson-Sosin modification of the Astler-Coller staging system and is described in Table 1.[6] The anatomic locations of the tumors within the large bowel were as follows: cecum, 27 patients; ascending colon, 12 patients; hepatic flexure, seven patients; transverse

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colon, three patients; splenic flexure, nine patients; descending colon, six patients; and sigmoid colon, 69 patients.

Postoperative radiation therapy was delivered *via* a Clinac 18 or 35 linear accelerator (Varian, Palo Alto, CA) by parallel opposed fields or appropriate arrangement of fields to treat the tumor bed with approximately a 5-cm margin with a total dose of 4500 cGy with 180 cGy fractions. This was followed by a shrinking field technique, sparing small bowel, to 5040–5500 cGy. Draining lymph nodes were included in the radiation field if they were felt to be at high risk of involvement. Technical aspects of treatment have been previously described.[5] Twenty-two patients were treated with adjuvant chemotherapy, generally with 5-fluorouracil (5-FU) alone.

Patients were evaluated for local failure, distant metastases, disease-free survival, and overall survival. Local failure was defined as a recurrence in the tumor bed and in adjacent organs by direct extension or in regional nodal groups. Regional nodal groups included lymph nodes up to the take-off of the colic vessels. Distant metastases were divided into abdominal and extra-abdominal failures. Abdominal failures included recurrences in the liver, peritoneal surfaces, para-aortic, and portahepatic lymph nodes (abdominal lymph nodes) but did not include tumor bed or regional nodal recurrences because these were classified as local rather than metastatic failures. Extra-abdominal failures included tumors in the lung, bone, central nervous system, or extra-abdominal lymph nodes. The 133 patients receiving postoperative radiotherapy were compared with a previously reported series of 395 patients with Stage B2, B3, C2, and C3 tumors who had surgical resection only at the Massachusetts General Hospital from 1970 to 1977.[3] The patients who had radiation therapy were unfavorably biased against radiation, however, because most were referred because of concern about the adequacy of local control with surgery alone. Actuarial local control and survival analyses were done by use of the Kaplan Meier method.[7]

TABLE 1. *Gunderson-Sosin Modification of stler-Coller Staging System*

Stage	Characteristics
A	Tumor limited to mucosa with nodes normal
B1	Extension through the muscosa but still within the bowel wall with nodes normal
B2	Extension through the entire bowel wall with nodes normal
B3	Extension through the entire bowel wall with adherence or invasion of adjacent organs or structures with nodes normal
C1	Lymph nodes with positive findings and tumor limited to the bowel wall
C2	Lymph nodes with positive findings and tumor through the entire bowel wall
C3	Lymph nodes with positive findings and extension through the entire bowel wall with adherence or invasion of adjacent organs or structures

Results

The 5-year actuarial local control, disease-free survival, and overall survival rates of all 133 patients receiving postoperative radiotherapy were 82%, 61%, and 62%, respectively. Table 2 shows by stage the 5-year actuarial local control, disease-free survival, and the overall survival rates for the patients who had postoperative radiotherapy and the patients who had surgery alone. With the exception of patients with Stage B2 disease, local control was at least 15% higher in the patients with Stage B3, C2, and C3 disease who had radiation therapy *versus* similarly staged surgical patients. Local control rates for patients with Stage B3, C2, and C3 disease receiving postoperative radiotherapy were 92%, 79%, and 69%, whereas these figures were 69%, 64%, and 47%, respectively, in patients having surgical resection only. Patients with Stage B3 and C3 disease receiving postoperative radiotherapy experienced a 13% and 12% increase in disease-free survival, respectively, relative to the group that had surgery alone. There was no improvement in disease-free survival rate for patients with Stage B2 or C2 disease.

The influence of the number of lymph nodes involved with carcinoma in the original specimen is shown in

TABLE 2. *Five-year Actuarial Local Control, Disease-free Survival, and Overall Survival Rates after Surgery Alone* Versus *Surgery Plus Radiation Therapy According to Stage*

	Surgery Alone				Surgery + Postoperative Radiotherapy			
Stage	No. Patients	Local Control Rate (%)	Disease-free Survival Rate (%)	Overall Survival Rate (%)	No. Patients	Local Control Rate (%)	Disease-free Survival Rate (%)	Overall Survival Rate (%)
B2	163	90	78	70	21	90	74	77
B3	83	69	64	63	37	92	77	81
C2	100	64	48	44	47	79	48	47
C3	49	47	38	37	28	69	50	51
Total	395	74	63	58	133	82	61	62

TABLE 3. *Five-year Actuarial Local Control, Disease-free Survival, and Overall Survival Rates after Surgery Alone* Versus *Surgery and Radiation Therapy (RT) of Patients with Stage C Disease According to Number of Lymph Nodes Involved*

No. of Nodes	Treatment	No. of Patients	Local Control Rate (%)	Disease-free Survival Rate (%)	Overall Survival Rate (%)
1	Surgery	68	66	58	58
	Surgery and postoperative RT	21	92	71	65
2–5	Surgery	65	58	36	32
	Surgery and postoperative RT	40	76	42	45
6–14	Surgery	16	26	20	13
	Surgery and postoperative RT	9	50	28	16

Table 3. Higher rates of local control, disease-free survival, and overall survival were seen in patients receiving postoperative radiotherapy as compared with surgery alone. However, the magnitude of the improvement was greatest in patients with involvement of only one lymph node.

Twenty-one patients had evidence of complete obstruction or perforation at the tumor site and received postoperative radiotherapy. There was an improvement in the local control and survival rates for the 13 patients with Stage B3 disease who had radiation therapy compared with the group that had surgery only (Table 4). The limited number of patients with Stage B2, C2, and C3 disease with obstruction or perforation receiving radiotherapy precludes any comparison.

Local failure occurred predominantly in the tumor bed in both the patients who had radiation therapy and those who did not. Nineteen patients had local failure after surgery and postoperative irradiation, with 17 of these occurring in the tumor bed and two concurrently in regional nodes and the tumor bed. This is similar to the failure pattern observed in patients who had resection alone.[3] Tables 5 and 6 show the pattern of failure in patients with surgery alone *versus* those with surgery plus postoperative radiotherapy. The development of distant metastases only was higher in the patients who had radiotherapy; however, the overall distant metastatic rates were similar in both groups (Table 5). The incidence of extra-abdominal and hepatic metastases, peritoneal seeding, or abdominal lymph node metastases was similar in the patients receiving and not receiving postoperative radiation therapy (Table 6).

Discussion

In rectal carcinoma, the natural history and failure patterns after resection are well known, and adjuvant radiation therapy has been shown to decrease local failure rates and increase survival rates.[8,9] Data supporting the use of adjuvant radiation therapy for the treatment of colonic carcinoma (tumors above the peritoneal reflection) are less clear. A number of studies have analyzed the failure patterns after surgical resection alone to identify subsets of patients at increased risk for local regional failure.[1-3] Gunderson et al. reported on 91 patients with Stage C1–C3 colonic carcinoma who had single and multiple reoperative procedures after initial resection and observed a 48% incidence of local regional failure.[1] Russell et al. reported the cases of patients with Stage A, B1, and C1 tumors having local failure rates of 10%; Stage B2 and C2 lesions, 11%; and Stage B3 and C3 tumors, 35%.[2] In the Massachusetts General Hospital surgical series, local failure was uncommon in Stage A, B1, B2, and C1 tumors, but for Stages B3, C2, and C3 the local failure rates were at least 30%.[3] From these data it would appear that adjuvant radiotherapy may be indicated for advanced stage colonic carcinoma, Stages B3, C2, and C3.

TABLE 4. *Five-year Actuarial Local Control, Disease-free Survival, and Overall Survival Rates for Patients with Completely Obstructive or Perforative Tumors*

	Surgery Alone				Surgery + Postoperative Radiotherapy			
Stage	No. Patients	Local Control Rate (%)	Disease-free Survival Rate (%)	Overall Survival Rate (%)	No. Patients	Local Control Rate (%)	Disease-free Survival Rate (%)	Overall Survival Rate (%)
B2	30	70	47	42	3	67	67	67
B3	26	39	35	42	13	100	84	84
C2	28	37	25	30	2	0	0	0
C3	13	55	34	37	3	67	67	67
Total	97	59	35	38	21	84	70	70

TABLE 5. *Stage* Versus *Failure Pattern*

	Local Failure Only		Distant Metastases Only		Local Failure and Distant Metastases	
Stage	Surgery	Surgery and Postoperative Radiation Therapy	Surgery	Surgery and Postoperative Radiation Therapy	Surgery	Surgery and Postoperative Radiation Therapy
B2	6/163 (4%)	0/21 (5%)	21/163 (13%)	3/21 (14%)	12/163 (7%)	2/21 (10%)
B3	9/83 (11%)	0/37 (0%)	6/83 (7%)	5/37 (14%)	16/83 (19%)	2/37 (5%)
C2	10/100 (10%)	2/47 (4%)	19/100 (19%)	14/47 (3%)	22/100 (22%)	4/47 (11%)
C3	6/49 (12%)	1/28 (4%)	4/49 (8%)	5/28 (18%)	18/49 (37%)	7/28 (25%)
Total	31/395 (8%)	3/133 (2%)	50/395 (13%)	27/133 (20%)	68/395 (17%)	16/133 (12%)

Published reports on the use of adjuvant postoperative radiation therapy for colonic carcinoma are limited by the small number of patients treated and short follow-up period. However, the data do suggest that local failure rates are reduced by postoperative radiotherapy and in some studies there was an improvement in survival rate when compared with that for historic controls. Loeffler reported on 10 patients with Stage B3–C3 cecal carcinomas who received adjuvant regional postoperative radiotherapy to doses of 6500–7500 cGy who were treated with two daily fractions of 70–75 cGy and observed no local failures.[10] However, five patients had distant metastases develop with follow-up of 7–76 months. Brenner et al. described 21 patients with Stage C colonic carcinoma who received whole abdominal radiotherapy to 2000 cGy in eight fractions with a boost dose of 2000–3000 cGy in 3 weeks to areas at high risk and concurrent weekly doses of 5-FU at 350 mg/m^2 intravenously (I.V.).[11] The patients who had radiation therapy were compared with a matched control group that had surgery alone, and a statistically significant improvement in the disease-free survival rate of 55% was observed in patients receiving radiation *versus* 12% in those who had surgery alone. Shehata et al. reported on 19 patients with Stage B2 (14 patients) and Stage C2 (five patients) cecal carcinoma treated with regional postoperative radiation therapy to 4500 cGy and weekly doses of 5-FU (600 mg/m^2 I.V.) and matched to a similar group treated with right hemicolectomy only and noted no statistical difference in the median survival or incidence of distant metastases.[12] However, the incidence of local failure was 5% in the patients who had radiation therapy *versus* 19% in the group that had surgery alone. Forty-eight patients with Stage B1–C2 colonic carcinoma received adjuvant postoperative local irradiation at the Princess Margaret Hospital.[13] For patients with Stage B1 and B2 tumors the local failure rate was three of 20 (15%), whereas for patients having Stage C1 and C2 lesions local failure was seen in nine of 23 patients (32%).

In this study, postoperative radiotherapy to the tumor bed to doses of at least 4500 cGy has reduced the incidence of local failure to 18% overall for these advanced staged patients. Stage for stage, the development of local regional failure was reduced for patients receiving postoperative radiotherapy compared with the historic control series. Local recurrences occurred in 8%, 21%, and 31% of patients with Stage B3, C2, and C3 tumors who had radiation therapy, whereas the local failure rates were 31%, 36%, and 53% in patients treated with surgery only. In addition, there was a 12–13% improvement in the 5-year disease-free survival rate in the patients with Stage B3 and C3 disease who had radiation therapy compared with historic controls. Although local failure rate was reduced in patients with Stage C2 carcinoma who had radiation therapy, there was no notable difference in the 5-year disease-free survival rate from the patients who had surgery only. However, there is a po-

TABLE 6. *Patterns of Distant Metastases after Surgery Alone* Versus *Surgery and Postoperative Radiotherapy*

			Extra-abdominal Failures		Liver		Peritoneal Seeding		Abdominal Lymph Nodes	
Stage	Treatment	No. of Patients	Only	Total	Only	Total	Only	Total	Only	Total
B2 and B3	Surgery	246	11 (4%)	28 (11%)	15 (5%)	35 (14%)	4 (2%)	9 (4%)	1 (1%)	5 (2%)
	Surgery and postoperative radiation therapy	58	2 (3%)	3 (5%)	8 (14%)	8 (14%)	1 (2%)	1 (2%)	0 (0%)	0 (0%)
C2 and C3	Surgery	149	7 (5%)	35 (23%)	13 (9%)	44 (30%)	4 (3%)	23 (15%)	2 (1%)	12 (8%)
	Surgery and postoperative radiation therapy	75	4 (5%)	13 (17%)	6 (8%)	17 (23%)	4 (5%)	11 (15%)	2 (3%)	8 (11%)

tential bias in this series in that patients referred for radiation therapy were those who were thought by the surgeon to have a higher risk of local failure. This can be seen by an analysis of the patients with Stage C disease, where 46% of the patients who had surgery alone had the good prognostic factor of only one positive lymph node compared with 30% of the patients who had radiation therapy. For the entire patient population, Stage B2 diseases represented 41% of the group that had surgery but only 16% of those who had radiation therapy and Stages C2 and C3 represented 25% and 12% of the patients who had surgery, respectively, but 35% and 21% of the group that had radiation therapy. Thus, by most parameters, there was a selection process for the patients with poorer prognoses to be sent for the adjuvant therapy.

The analysis of patients with Stage C disease by the number of lymph nodes with carcinoma in the specimen showed that the patients with only one node involved who had radiation therapy had similar local control and disease-free survival rates as patients receiving postoperative radiotherapy for Stage B3 disease, which were clearly superior to those of the patients who had resection only. With increasing nodal involvement, local control and disease-free survival rates decreased progressively; however, local control and disease-free survival rates appeared higher with irradiation.

Local failures after resection and postoperative radiotherapy or surgery alone occurred predominantly in the tumor bed and not in regional nodes. Rates of failure in liver, peritoneal surfaces, abdominal lymph nodes, and extra-abdominal sites were similar among the two groups of patients.

For patients with Stage B2 disease there did not appear to be a notable gain in local control or disease-free survival rates in the patients who received radiation therapy *versus* the historic control patients. This is as expected, because the more recent analyses of failure patterns after surgery alone have not shown a high local failure for patients with Stage B2 disease without obstruction or perforation. In view of the reduction in local failure and improved disease-free survival rates in patients who had radiation therapy, we think that adjuvant postoperative irradiation for patients with Stage B3, C2, and C3 tumors is a promising approach that needs to be investigated through a prospective randomized trial.

Despite improvements in local control in the patients who had radiation therapy, the local failure rates were still significant for patients with Stage C disease with involvement of two or more lymph nodes (24% or greater). At the present time, all patients having postoperative irradiation are receiving 3 days of concurrent 5-FU at 500 mg/m^2/day I.V. for 3 days at the start and the completion of radiation therapy. Because the adjuvant studies of rectal carcinoma have shown the greatest survival and local control advantage with the combined use of radiation and chemotherapy, it is very possible that this combination will also be effective in colonic carcinoma.[8] Consideration of intraoperative radiation therapy for selected high-risk patients may also be used as a means of increasing the dose to the tumor bed to reduce further local failure and perhaps to increase disease-free survival. Ongoing studies will clarify the value of these treatment modalities.

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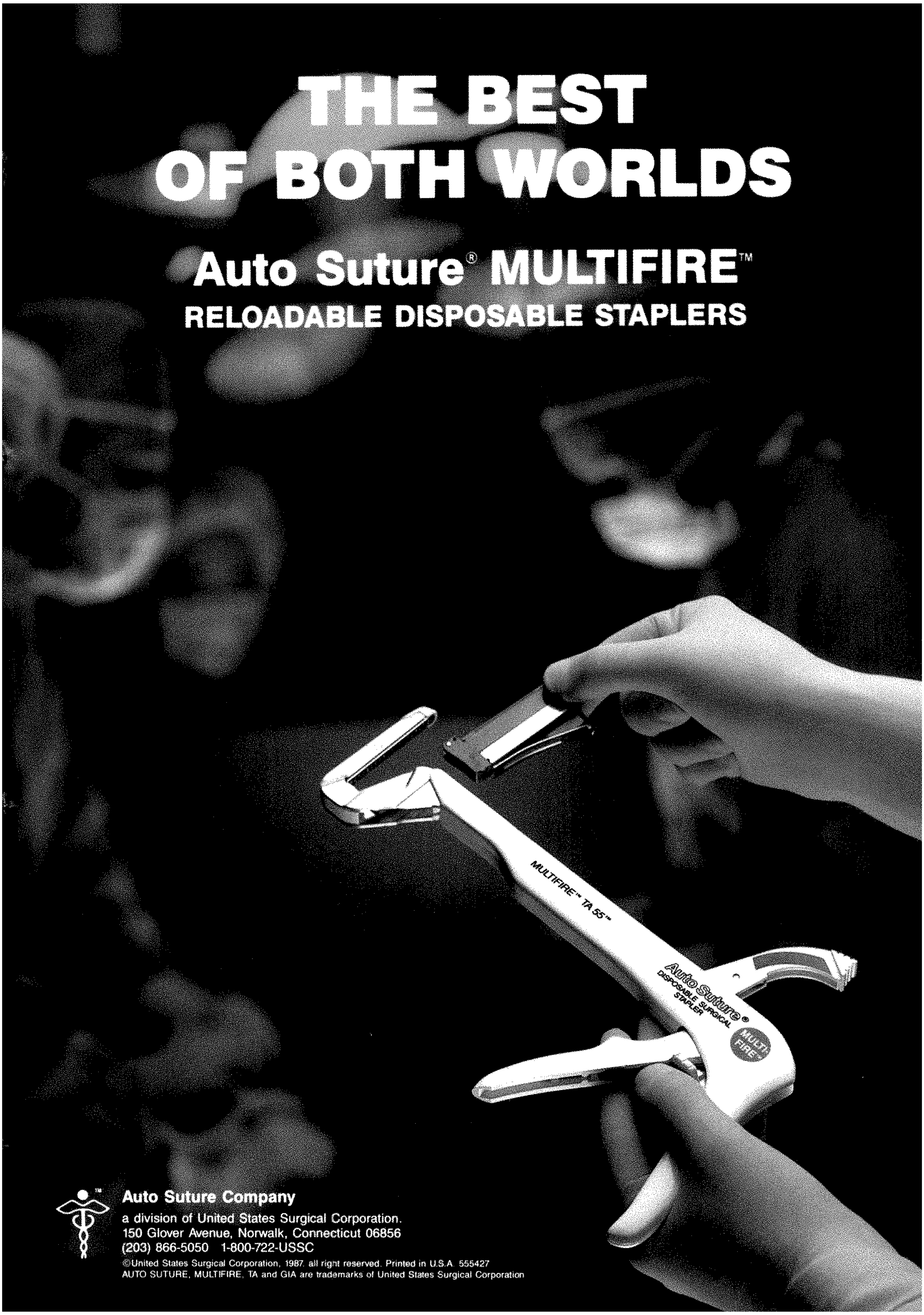

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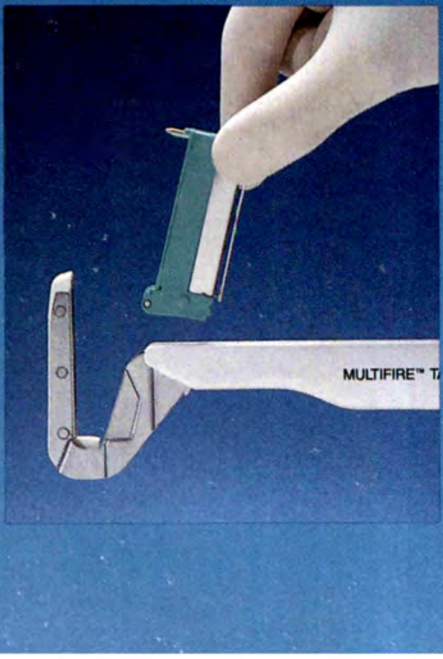

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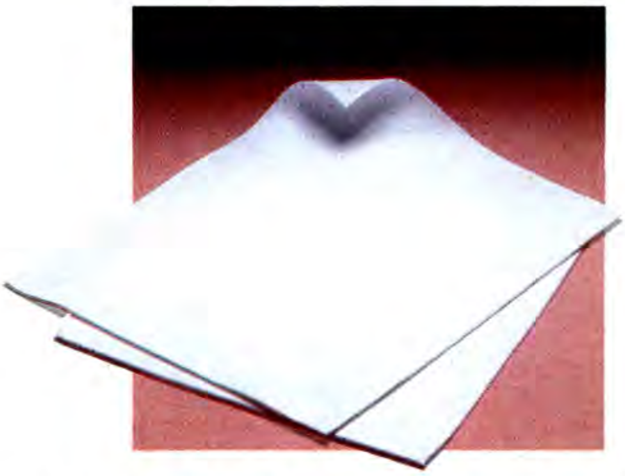

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Pyogenic Liver Abscess

Diagnostic and Therapeutic Strategies

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A retrospective review of 26 adult patients admitted to University of California, Davis, Medical Center (UCDMC) with pyogenic liver abscess (1980–1986) was performed to ascertain the impact of rapid diagnosis and percutaneous drainage. Ultrasonographic examinations and computed tomography (CT) scans were highly sensitive and noninvasive imaging modalities. Sixteen patients had solitary abscesses and seven had multiple microscopic abscesses. The median time interval from admission to diagnosis and therapy was 2 and 3 days, respectively. Origin of the abscess was determined in 22 patients, the biliary tree being the most common source. Medical therapy was successful in three patients with microabscesses but failed in two. Nine patients had percutaneous drainage; two required repetitive percutaneous catheter placement, and two proceeded to surgical drainage. Twelve patients had surgical drainage; one required repetitive surgical drainage. Postdrainage complications were minimal in all groups. Overall mortality role was 11.5% (two patients). Deaths were related to delay in diagnosis, gram-negative sepsis at presentation, and biliary origin of the abscess.

RECENT REPORTS have emphasized the changing epidemiology, treatment, and prognosis of pyogenic liver abscess.[1-6] The availability of imaging modalities, ultrasonography, and computerized tomography (CT) and the successful application of closed percutaneous drainage of pyogenic liver abscess have changed approaches to diagnosis and therapy. We report our 6-year experience with pyogenic liver abscess with emphasis on diagnostic and therapeutic strategies.

Patients and Materials

Between January 1, 1980, and June 30, 1986, 26 patients older than the age of 16 years of age were admitted to University of California, Davis, Medical Center (UCDMC) with a final diagnosis of pyogenic liver abscess confirmed microbiologically and/or pathologically. UCDMC is a 453-bed University-based teaching hospital. Pediatric patients (N = 4) with pyogenic liver abscess and adult patients with amebic liver abscess (N = 14) identified during this time period were excluded from analysis. The case records of these 26 patients were reviewed with particular care devoted to ascertaining clinical features, time interval to diagnosis and therapy, imaging studies, microbiology, initial treatment, necessity for retreatment, and outcome.

Results

Clinical and Laboratory Features

Nineteen patients were men and seven were women. Their ages ranged from 21 to 76 years, with a mean of 47. Six patients were referred from other institutions. APACHE II scores, a physiologic measure of the severity of illness, ranged from 0 to 33, with a mean of 9.3.[7] More common signs and symptoms are shown in Table 1, and initial laboratory findings are shown in Table 2. Fourteen of the 26 patients had one or more co-morbid factors (biliary disease, malignancy, drug-related immunosuppression, diabetes mellitus, recent abdominal surgery, or chronic alcoholism). The initial chest roentgenogram abnormalities included atelectasis, hemidiaphragmatic elevation, or pleural effusion at the right base in 13 patients.

Diagnosis

Twenty-five of the 26 patients were diagnosed before death. The median number of days the patients had symptoms before hospitalization was 14 (range: 1–120 days). In six patients the diagnosis was made before hos-

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TABLE 1. *Clinical Features (N = 26)*

	No.	(%)
Symptoms		
Fever	23	(88)
Nausea/malaise	18	(69)
Weight loss	15	(58)
Abdominal pain	10	(38)
Signs		
Fever	25	(96)
RUQ tenderness	16	(62)
Hepatomegally	10	(38)
Jaundice	3	(12)

pitalization. In the remaining patients, the most common types of tentative diagnoses and symptoms cited on admission were cholecystitis, fever and abdominal pain, and sepsis of unknown source. Diagnosis was usually made after ultrasonography or CT scan for evaluation of abnormal liver enzymes, right upper quadrant tenderness, or chest roentgenographic abnormalities. Median length of patient hospital stay before a diagnosis was established was 2 days (range: 0–8 days). Thirteen patients had diagnostic aspiration or drainage before definitive therapy. Purulent material was aspirated in all patients, and there were two complications (one ruptured abscess necessitating immediate surgery and one hemorrhage necessitating transfusion).

Noninvasive Imaging

The initial imaging study is shown in Table 3. Ultrasonographic examination performed in 17 patients and the findings were positive in 15. In one patient a single abscess was missed and in another the ultrasonographic examination showed a single abscess in a patient with multiple abscesses. Both of these patients had nonhomogeneous liver scans secondary to co-existing liver disease. The initial procedure was CT scan for six patients and sulfur colloid scanning in two patients. There were no false-negative results in either group. One patient had an exploratory laparotomy that had normal findings. After operation an ultrasonographic examination was performed that indicated an abscess.

Most patients had multiple imaging studies during therapy. Both ultrasonographic examination and CT scan were highly specific, and we found little difference in terms of information obtained from the two modalities when used in follow-up examinations.

Abscess Characteristics

Three patients had multiple microabscesses (less than 1.5 cm), all of whom had a clinical picture of ascending cholangitis. Sixteen patients had solitary liver abscess, and seven patients had multiple abscesses (29 macroscopic abscesses in 23 patients). Twenty-three of the 29 macroabscesses were located in the right lobe. Eleven abscesses were between 1.5 and 5 cm, 12 abscesses between 5 and 8.0 cm, and six abscesses were greater than 8.0 cm. Twelve of 29 abscesses appeared loculated by ultrasonographic examination or CT scan, although these loculations were confirmed at subsequent drainage in only two patients.

Microbiology

All 26 patients had positive abscess culture results despite that they had received broad-spectrum antibiotics at the time of the initial culture of the liver abscess (Table 4). A total of 56 different organisms were isolated in 26 patients. Eight patients (31%) had monomicrobial cultures. Two organisms were isolated in 10 patients, three organisms in five patients, four organisms in two patients, and five organisms in one patient. As expected, the bacteriologic study showed a predominance of gram-negative aerobes (22 of 56) and anaerobes (27 of 56). Blood culture results were positive in nine of the 19 patients from which they were obtained.

Origin of Pyogenic Abscess

The origin of the pyogenic liver abscess was eventually determined in 22 (85%) patients (Table 5). In 14 patients the source was evident at diagnosis and was known before therapy was initiated. Clinical history and ultrasonographic or CT imaging were most helpful in determining origin, especially as it pertained to the biliary tree. In the remaining 12 patients the source was not evident at the time of therapy but was determined in

TABLE 2. *Laboratory Findings*

	Mean	Range	Percentage	Abnormal
Hemoglobin (g/L)	11.8	8.0–15.4	62	(<12 g/L)
Leukocyte count (per mm^3)	16,600	7,00–31,000	73	(>10,000/mm^3)
Alkaline phosphatase (IU/L)	462	77–3774	73	(>115 IU/L)
GGTP (IU/L)	236	15–1500	73	(100 IU/L)
Albumin (g/dL)	3.0	1.4–4.6	69	(<3.5 g/dL)
Bilirubin (mg/dL)	1.98	0.2–13.7	23	(>1.4 mg/dL)
Serum glutamic oxaloacetic transaminase (IU/dL)	83.5	19–580	31	(>40 IU/dL)

TABLE 3. *Initial Imaging Study*

	No.	(%)	Positive Results	Negative Results
Ultrasound	17	(65)	15	2
Computed tomography	6	(23)	6	0
Scintiscan	2	(8)	2	0
Laparotomy	1	(4)	0	1

* Percentage of total number.

TABLE 4.

Organisms	Monomicrobial Isolates (8 Patients)	Polymicrobial Isolates (18 Patients)	Total
Gram-negative aerobes			
E. coli	4	8	12
Klebsiella	0	4	4
Proteus	0	2	2
Serratia	0	1	[illegible]
Morganella	0	1	[illegible]
Acinetobacter	0	1	1
Eikinella	0	1	1
Gram-positive aerobes			
Streptococcus faecalis	0	4	4
β-Streptococcus	0	2	2
α-Streptococcus	1	0	1
Gram-negative anaerobes			
Fusobacterium nucleatum	1	4	5
B. fragilis	0	7	7
Bacteriodes species	0	3	3
"Anaerobic gram-negative cocci"	0	1	1
Gram-positive anaerobes			
Peptostreptococci	0	6	6
Anaerobic diphtheroids	2	2	4
Lactobacillus	0	1	1

eight patients during the course of therapy. A barium enema was performed in six patients, which showed recent evidence of perforated diverticulum in two patients and extensive diverticular disease in another. Endoscopic retrograde cholangiopancreaticography was performed in four patients and had normal findings in all cases. The origin could be determined at laparotomy in three patients, with further clinical evaluation in one patient, and at necropsy in an additional patient.

Nine liver abscesses (35%) originated in the biliary tree, seven from cholecystitis and/or cholangitis and two from malignant obstruction of the biliary tree. Of the five cases originating from the colon, the origin was only evident in two patients on admission. Local penetrating trauma accounted for three cases and seeding from a source of infection in a distant location in three other patients. No source could be determined in four patients, despite a thorough investigation.

Therapy and Outcome

All patients generally received broad-spectrum antibiotics before diagnosis. The median time from admission to initiation of antibiotic therapy was 1 day (range: 0–8 days). The median time from admission to a drainage procedure was 3 days (range: 1–8 days). The initial treatment and requirement for retreatment for the 26 patients are shown in Table 6. In one patient, a diagnosis of liver abscess was not made before death. The patient received continuous antibiotics as the sole treatment, and an abscess was discovered at necropsy. One patient had a single aspiration followed by antibiotics. The abscess re-accumulated and was successfully treated by closed continuous percutaneous drainage.

Nine patients, three of whom had multiple abscesses, were initially treated by closed, continuous percutaneous drainage. All were clinically and hemodynamically stable. Diagnostic aspiration was followed by placement of a 7–12 Fr pigtail catheter by use of a modified Seldinger technique.[8] Catheter placement was carried out under guidance with either ultrasonography or CT scan. Once the catheter was adequately positioned, saline irrigation was performed and the drains were placed to gravity drainage. One drain was placed per abscess cavity. Patients were monitored by CT scan or ultrasonography to ensure complete drainage. The drains were left in for an average of 8 days (range: 4–18 days) and removed when the abscess cavity had collapsed around the catheter. Percutaneous drainage was considered to have failed if any of the following were noted: (1) complications related to catheter insertion that necessitated surgical intervention; (2) lack of improvement or worsening condition after 72 hours of percutaneous drainage; and (3) recurrence of the abscess within 3 months of therapy. Four patients' percutaneous drainage failed (Fig. 1). Two of these were treated successfully by placement of a second percutaneous catheter, and one patient went directly to successful surgical drainage. A blood clot was found in the abscess cavity. Another patient had successful surgical drainage after failure of a second percutaneous catheter drainage attempt. There were no

TABLE 5. *Origin of Pyogenic Abscess*

	At Time of Therapy	Determined During Therapy	Total
Cholecystitis/cholangitis	5	2	7
Biliary tract malignancy	2	0	2
Colon	2	3	5
Local penetrating trauma	3	0	3
Hematogenous seeding	0	3	3
Recent gastric or duodenal surgery	2	0	2
Unknown	—	4	4
Total	14	12	26

TABLE 6. *Therapy and Outcome*

Initial Therapy	No. of Patients	Outcome (No. of Patients) Cure	Treatment Failure	Death	Comments
Medical therapy					
Antibiotics alone	1	0	0	1	Diagnosis not established before death
Single aspiration and antibiotics	1	0	1	0	Percutaneous drainage successful in treatment failure
Antibiotics, cholecystectomy, or removal of T-tube	3	3	0	0	All with multiple microabscesses and ascending cholangitis
Drainage procedure					
Percutaneous drainage and antibiotics	9	5	4	0	Two patients treated with percutaneous catheter; two patients taken to surgical drainage (see text)
Surgical drainage and antibiotics	8	5	1	2	See text
Cholecystectomy, surgical drainage, and antibiotics	4	4	0	0	—

deaths in this group. Two complications were seen in the 13 patients who had diagnostic aspiration; abscess spillage necessitating immediate surgery occurred in one patient and hemorrhage necessitating transfusion in another. No complications arising from therapeutic drainage were seen.

Twelve patients had surgical drainage as initial therapy. Four patients with cholecystitis recognized on admission were successfully treated with cholecystectomy and operative drainage of the abscess. The other eight patients had operative drainage for a variety of reasons. In two of these patients, a single aspiration followed by treatment with antibiotics had failed at another hospital. One patient had an acute abdomen, one had spillage during diagnostic aspiration, and for four, two of whom were gravely ill, it was the clinician's choice. There was one treatment failure and two deaths in the patients that had surgical drainage. One patient had successfully repetitive surgical drainage 10 days after the first drainage, when the abscess failed to resolve. Another patient, in whom diagnosis was delayed, died after surgical drainage. The other patient died during operation for multiple abscesses. Two of the three patients with microabscesses were successfully treated with cholecystectomy, T-tube drainage, and antibiotics. The other patient was treated by antibiotics and removal of a T-tube previously placed.

The overall deaths were three of 26 (mortality rate: 11.5%). Analysis of the three deaths showed three common features: significant delay in diagnosis and treatment, high APACHE II scores, and origin of the abscess from the biliary tree. The patient that was diagnosed after death had an acute abdomen and sepsis. Exploratory laparotomy did not reveal any abnormalities. Blood cultures were positive for *Escherichia coli,* and the patient died from sepsis on the 10th hospital day. Necropsy showed a pyogenic abscess deep in the liver parenchyma associated with cholangitis. Culture of the biliary tree and abscess grew a pure culture of *E. coli.* In the other two deaths, there was a significant delay in diagnosis (7 and 8 days). One patient died during operation for multiple abscesses that surrounded the inferior vena cava, and the other patient died from multiorgan failure 14 days after surgical drainage. The mean APACHE II scores of the patients that died was 26.3 compared with 7.1 for the group of patients that were cured. Of the 23 surviving patients, follow-up information was available in 17 patients at 6 months without evidence of recurrence.

Discussion

In this review, we have been able to assess the impact of both imaging modalities (CT scanning and ultraso-

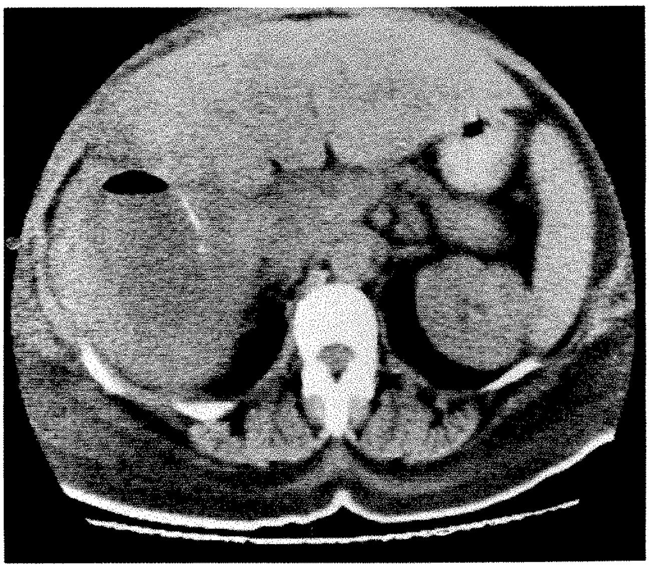

FIG. 1. Pyogenic abscess for which two efforts at percutaneous drainage failed.

nography) in expediting the diagnosis and the effect of percutaneous drainage on the clinical course and outcome of patients with pyogenic liver abscess. Most previously reported series include patients from several decades before the advent of these new techniques.[1-3,5,10]

The clinical presentation of pyogenic liver abscess remains insidious and may be protracted. Often the signs on physical examination and symptoms of a liver abscess are nonspecific; in our experience, the cholestatic pattern of liver function enzyme abnormalities is suggestive but not specific of a hepatic abscess. Fever, right upper quadrant tenderness, elevated venous leukocyte count, and hypoalbuminemia are present in most patients. The use of the APACHE II scoring system proved useful in identifying patients with a poor outcome.

The microbiologic findings for this group of patients showed the usual predominance of anaerobes and gram-negative aerobic bacilli. Since the advent of anaerobic cultures, non–spore-forming anaerobic bacteria have been recognized as important pathogens in pyogenic liver abscess and are recovered in 25–45% of cases.[11] We observed polymicrobial isolates in 69% of patients. Earlier studies have reported an increase in mortality rate with polymicrobial isolates,[3] although we did not observe this event in this small series. Bacteriologic results are generally not helpful in identifying the source of the pyogenic liver abscess, although multiple anaerobic isolates point to the colon as a source and a single isolate of *E. coli* often indicates the biliary tree as a nidus.

The optimal choice of antibiotics in liver abscess is unknown, although experimental evidence supports the use of agents active against both gram-negative aerobes and anaerobes. Most anaerobes originating in the abdomen are susceptible to similar antibiotics, and sensitivity testing is unreliable in routine anaerobiologic laboratories. The traditional use of an aminoglycoside combined with clindamycin or metronidazole is still recommended.[13] Both metronidazole and clindamycin have wide anaerobic coverage, excellent penetration to abscess cavities, and minimal side effects with short-term use. Third-generation cephalosporins have excellent activity but lack coverage for some gram-negative aerobes and anaerobes, especially *Bacteroides fragilis* (which was present in seven of our patients). The final choice of antibiotics should be guided by a culture. The duration of antibiotic therapy is controversial, but we agree with many reports that recommended therapy for 6 weeks.[14,15] When there is adequate drainage, we also feel that antibiotics should be given for 7 days after resolution of the abscess cavity and clinical signs of toxicity.

With the use of modern imaging procedures, the ability to diagnose pyogenic liver abscess is markedly improved from the past. In early studies, as many as 30% of patients with hepatic abscesses were diagnosed after death, whereas in this study 25 of 26 patients were diagnosed before death. The median time from admission to diagnosis was 2 days, which is a significant improvement from even recent studies that report the time to diagnosis range from 6.5 to 23 days.[3,16] We attributed this improvement to the sensitivity and accuracy of ultrasonography and CT scanning and aspiration of the abscess. Diagnosis is now possible with a high degree of certainty without surgical confirmation. Ultrasonography has a reported sensitivity of detecting pyogenic liver abscesses in the range of 85–95% and CT scanning of 95–100%.[17,18] Ultrasonography has the advantage of accurately visualizing the biliary tree and is better than CT scanning in distinguishing solid from cystic structures, but ultrasonography is limited by technical factors. Certain areas of the liver are difficult to visualize by ultrasonographic examination. These include areas adjacent to the hemidiaphragm, where visualization is difficult when the liver is anatomically situated high under the rib cage. Extremely obese patients and those who are uncooperative are difficult to scan with ultrasonography. Two false-negative results by ultrasonography in this study were in patients with nonhomogenous livers. In this regard, the CT scan is more sensitive and can distinguish subtle differences in density. CT scanning also has the advantage of visualizing the posterior, superior aspect of the liver. The CT scan best demonstrates surrounding structures, but both ultrasonography and CT scanning may be used to look for sources of sepsis outside the liver (i.e., kidney). Because of the common association of pyogenic liver abscesses with biliary disease, both ultrasonographic examination and CT scans may be useful to identify cholelithiasis or biliary obstruction. The technetium scan[17] adds little to the information available from ultrasonographic examination and CT scan and should never be used alone in assessing suspected liver abscesses.

Neither ultrasonography or CT scanning are accurate in differentiating loculations from multiple separate liver abscesses. Because it is requisite to drain all liver abscesses when there is more than one, any significant loculation may necessitate placement of a second catheter to improve drainage. Gerzoff et al.[19] and Bernardino et al.[20] reported that most loculations seen by ultrasonographic examination or CT scans are pseudoloculations and communicate freely within the abscess cavity. When significant loculations occur, they can potentially be a source of an inadequate percutaneous drainage and treatment failure but are not contraindications to percutaneous drainage.[21]

Determination of the origin of pyogenic liver abscess is important because it impacts on therapy. In this study the origin was determined in 14 of 26 patients at the time of therapy and later in the other eight patients. Barium enema was useful in this small series in detecting occult colonic disease, especially peridiverticular abscess. The source of the abscess was not apparent even after extensive investigation in four patients. So-called cryptogenic liver abscesses account for approximately 20% of cases, even in recent studies.[10] Biliary tract disease accounted for nine cases and is the most common underlying origin being reported.[1,22] Malignant biliary tract obstruction is becoming an increasingly significant source for pyogenic liver abscess.[3]

The source and characteristics of the abscess and the patient's underlying clinical condition are important parameters in determining therapy.

It appears that multiple microabscesses will predictably respond to systemic antibiotics.[23] However, it is important to determine the source of such abscesses because multiple small abscesses usually occur with co-existing cholangitis. In this series all three patients with multiple microscopic abscesses had ascending cholangitis necessitating additional corrective surgery on the biliary tree.

For single or multiple macroscopic abscesses, it is becoming increasingly clear that continuous drainage is necessary, either surgically or percutaneously. Since the report of McFazedean et al.[24] report in 1953, there has been controversy over the role of medical management alone in the treatment of pyogenic liver abscess. Subsequently, there has been a number of case reports[14,25–28] of the successful therapeutic management of pyogenic liver abscess without a drainage procedure (antibiotics alone or a single aspiration followed by antibiotics). In this series the one patient who did not have a drainage procedure because of failed diagnosis died later, despite continuous antibiotic therapy. In another patient, single aspiration followed by antibiotics was unsuccessful. In two referred patients single aspiration followed by antibiotic treatment had failed. McKorkell and Niles[29] reported on a series of 14 patients that medical management was successful in only one patient and concluded that medical management is not likely to be successful. In other studies[4,9,10,16] mortality rates for patients not receiving drainage procedures ranged from 70 to 100%. Although medical management may be successful in a small percentage of patients, we believe that continuous drainage is required for optimal therapy.

The experience with the use of closed continuous percutaneous drainage of pyogenic liver abscess continues to expand.[5,13,19,20,30–33] Initial studies reported a high success rate with few complications. Nine of our patients had percutaneous drainage as the initial procedure, and it was unsuccessful in four (44%). In three of these patients the failure of the abscess to resolve necessitated the placement of a second percutaneous catheter. The failure rate and complications of percutaneous drainage of pyogenic liver abscess have been reviewed in the English literature,[19] with a reported failure rate of approximately 15% and a complication rate of 4%. Because of the high success rate, particularly in gravely ill patients, closed continuous percutaneous drainage should be the initial drainage procedure, provided there is no other indication for laparotomy and percutaneous drainage is technically feasible.[34] For those patients in whom the source of the abscess is not obvious, percutaneous drainage can be used as a temporizing measure. The optimal time of catheter removal is not known. We have adopted a policy of obtaining serial imaging studies and removing the catheter when the abscess cavity has collapsed around the catheter and drainage has ceased. Many studies reported the time to catheter removal to be between 16 and 20 days, although Johnson et al.[33] reported successful treatment of pyogenic liver abscess with only 3–4 days of catheter drainage.

Laparotomy with surgical drainage has an important role in the management of pyogenic liver abscess. Although studies from the era before CT scans and ultrasonic imaging reported a significant mortality rate with operative drainage, these historic observations are no longer valid because of improved preoperative, operative, and postoperative care as well as more timely diagnosis. Operative drainage is highly effective and now has a low mortality and morbidity rates in the management of patients with pyogenic liver abscess. There are no controlled studies comparing percutaneous with operative drainage of liver abscesses. In patients with an identified intra-abdominal source of the liver abscess as an indication for laparotomy, surgical drainage is the procedure of choice. For abscesses in which percutaneous drainage has failed or abscesses in which percutaneous drainage is not technically feasible, surgical drainage is the preferred treatment. Furthermore, surgery is often essential in eliminating the source of infections that seeded the liver, as was necessary in eight of the 12 patients coming to operation.

Overall, three of 26 patients in this study died (mortality rate: 11.5%). In an analysis of the three deaths, we found delay in diagnosis, a biliary source, and a high APACHE II score were significant factors. Other authors have reported a mortality rate of 10–20%, which has significantly improved even from reports of 10 years ago. We feel this improved mortality rate reflects the improved capability for early diagnosis and rapid application of therapy. Successful management of pyogenic liver abscess entails an individualized approach based on the underlying clinical condition and source of the abscess and rapid institution of therapy. The reduced mortality rate of pyogenic liver abscess reflects the improved capability of rapid diagnosis and individualized therapy based on underlying severity of illness and knowledge of the source of the abscess.

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Gastrointestinal Sarcomas

Analysis of Prognostic Factors

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Clinical and pathologic data from 51 patients with primary sarcomas of the gastrointestinal tract treated from 1951 through 1984 were reviewed to determine clinical presentation, histologic features, treatment, and prognostic factors. The most common signs and symptoms were abdominal pain (62%), gastrointestinal bleeding (40%), and/or abdominal mass (38%). The primary site was stomach in 50%, small bowel in 30%, colorectum in 15%, and esophagus in 5%. Virtually all the sarcomas were leiomyosarcomas. Distribution was uniform among the three histologic grades; although 88% of Grade 1 tumors could be completely excised, only 35% of Grade 3 tumors could be completely resected. The 5-year survival rate was 75% for Grade 1 tumors, 16% for Grade 2 tumors, and 28% for Grade 3 tumors ($p = 0.0013$, Grade 1 *vs.* 2 and 3). Thirty of the 51 patients (59%) had curative resection with an operative morbidity rate of 24% and an operative mortality rate of 12%; at 5 years the disease-free survival rate was 58% and the overall survival rate was 63% (48% at 10 years). Eleven patients (42%) had recurrent disease develop at a median interval of 2 years after complete tumor excision. Twenty-one patients (41%) had partial excision or biopsy only of their tumors with an operative morbidity rate of 28%, operative mortality rate of 8%, and median survival of only 9 months. Overall, patients whose tumors were confined to the site of origin had a 58% 5-year survival rate compared with 20% for those whose tumors had invaded adjacent organs ($p < 0.05$). If the tumor was less than 10 cm in size, the 5-year survival rate was 78%, significantly better than the 38% for tumors greater than 10 cm ($p = 0.03$). These data suggest that histologic grade, local invasiveness, size, and extent of resection are the most important prognostic factors for patients with primary gastrointestinal sarcomas. Patients who have resection of all gross tumor, especially if it is well differentiated and localized, have a good prognosis.

GASTROINTESTINAL SARCOMAS are uncommon tumors, constituting 1–2% of all gastrointestinal malignancies and about 10% of all sarcomas.[1,2] The literature consists mostly of isolated case reports, and only a few studies of gastric or intestinal leiomyosarcomas from any one institution are reported. There is wide variation in reported survival rates and no uniform therapeutic approach. However, in recent years there has been considerable progress made in the pathologic interpretation of soft tissue sarcomas in general, thus enabling a more accurate assessment of prognostic variables.

The purpose of this review is to analyze the management of primary gastrointestinal sarcomas at the Medical College of Virginia (MCV), to delineate their natural history, and to investigate the influence of various factors on prognosis.

Materials and Methods

Fifty-one patients were treated at MCV from 1952 to 1984 for primary gastrointestinal sarcomas. Pediatric rhabdomyosarcomas have been excluded from this study because of their different natural history since the advent of combined modality therapy.[3] Charts and histopathologic slides were reviewed to determine clinical presentation, histologic type and grade of the tumor, extent of surgical resection, operative morbidity and mortality rates, the use of radiation and/or chemotherapy in addition to surgery, pattern of recurrence and metastases, and survival data.

For the purpose of this review, resection was considered complete if all gross disease was removed and the microscopic margins were tumor-free. Partial resection included those cases in which the bulk of tumor was removed but gross or microscopic disease remained.

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TABLE 1. *Histopathologic Grading of Gastrointestinal Sarcomas*

Grade 1	Well differentiated Moderate cellularity Lack of anaplasia 0–4 mitoses/10 high-power fields
Grade 2	Moderately differentiated Moderate cellularity Mild anaplasia 5–9 mitoses/10 high-power fields
Grade 3	Poorly differentiated Marked cellularity Marked anaplasia ≥10 mitoses/10 high-power fields

Survival curves were plotted by use of Cox's proportional hazards model.[4]

The histologic slides were characterized in terms of differentiation, cellularity, anaplasia or atypia, and mitotic index. These tumors were then graded according to the criteria indicated in Table 1.

Results

Clinical Presentation

The mean age of the patients with gastrointestinal sarcomas was 53 years (range: 9–83 years). There was a slight male predominance, with a ratio of 1.8:1. The most common presenting complaint was abdominal pain, which was present in 62% of the patients. Forty per cent of the patients had evidence of gastrointestinal blood loss. Thirty-six per cent of patients had significant weight loss, and 28% complained of anorexia, nausea, or vomiting. The average duration of symptoms was 4.4 months (range: less than 1–24 months). An abdominal mass was palpable on physical examination in 38% of the patients (Table 2).

The average diameter of tumors was 11 cm (range: 1.5–23 cm). The tumors were slightly smaller in those patients having complete resection, but this was not statistically significant.

The distribution of the gastrointestinal sarcomas according to location is shown in Table 3. More than half of the tumors were located in the stomach, with 14 in the small intestine, eight in the colorectum, and only three in the esophagus.

TABLE 2. *Presenting Signs and Symptoms of Patients with Gastrointestinal Sarcomas*

Signs and Symptoms	No. of Patients	Percentage
Abdominal pain	31	62
Gastrointestinal bleeding	20	40
Abdominal mass	19	38
Weight loss	18	36
Anorexia, nausea, and vomiting	14	28

TABLE 3. *Distribution of Gastrointestinal Sarcomas*

Site	Number	Percentage
Esophagus	3	6
Stomach	26	51
Duodenum	3	6
Jejunum	7	13
Ileum	4	8
Colon	5	10
Rectum	3	6
Total	51	100

Histopathology

Virtually all the tumors were leiomyosarcomas, of which 44 were spindle cell type and five were epithelioid cell type (also known as malignant leiomyoblastoma). There was one malignant fibrous histiocytoma located at the base of the appendix and one hemangiopericytoma located in the sigmoid colon, representing extremely rare locations for these histologic types.

Table 4 shows the distribution of histologic grade in terms of those patients having complete *versus* partial resection of their tumors. Although there was a near uniform distribution of tumors between the three tumor grades, there was a marked difference in the extent of surgical resection possible among the three groups classified by grade. Almost all the patients with Grade 1 tumors could have complete resections, whereas only one-third of the Grade 3 tumors could be resected completely.

Extent of Surgery

Thirty of the 51 patients (59%) had complete resection of their tumors. These patients had 33 operations in which their tumors were completely excised; 27% of these operations necessitated resection of adjacent organs to ensure adequate margins. The most frequent adjacent organs resected were spleen and tail of pancreas (in association with gastric sarcomas); there was one pancreaticoduodenectomy plus nephrectomy performed to completely excise a sarcoma of the duodenum. There was a 24% incidence of postoperative complications in these patients, the most frequent being wound infections and sepsis. There were four deaths (12% operative mortality rate) among those patients having complete excision; three of those resulted from

TABLE 4. *Histologic Grade of Gastrointestinal Sarcomas*

	Grade 1	Grade 2	Grade 3
Complete excision	14	11	5
Partial excision	2	10	9
Total	16	21	14

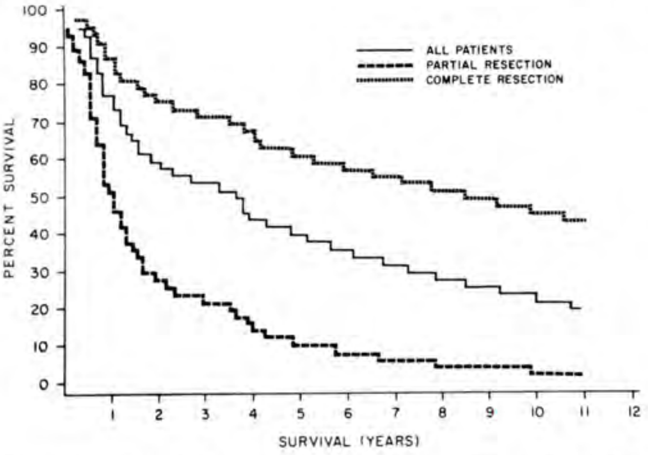

FIG. 1. Actuarial survival curves for patients having complete or partial resection of primary gastrointestinal sarcomas.

sepsis and occurred during the first 6 years of the review. The other death resulted from breakdown of the gastrojejunostomy and overwhelming sepsis in the patient who had a pancreaticoduodenectomy.

Twenty-one patients (41%) had 25 operations with partial excision or biopsy only of their tumors; the morbidity rate was 28% and operative mortality rate was 8% in this group of patients having palliative operations.

Pattern of Recurrence and Metastases

Twelve of the 26 patients (46%) who survived complete resection had recurrent disease develop. The recurrence was initially local in three patients; 10 of the 12 patients eventually had distant metastatic disease develop. The median interval from initial resection to detection of recurrence in these 12 patients was 2 years (range: 6–98 months). The three patients whose recurrence was local had complete excision of the recurrent tumor, with one patient surviving 16 years with no evidence of disease and the other two patients dying from recurrent tumor 12 and 31 months after re-excision.

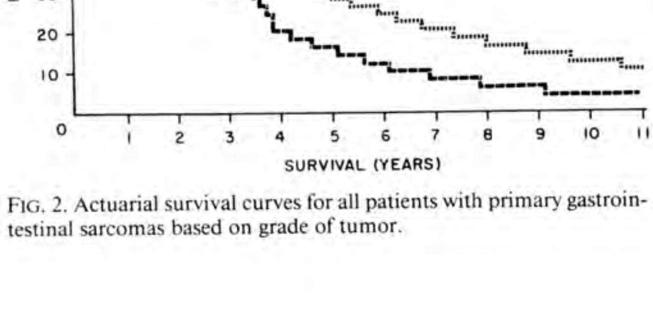

FIG. 2. Actuarial survival curves for all patients with primary gastrointestinal sarcomas based on grade of tumor.

Twenty-eight of the 51 patients (55%) had documented distant metastases or subsequently had them develop. The most common sites of metastases were liver (65%), peritoneum (43%), regional nodes (28%), and omentum (18%). There were only three cases of extra-abdominal metastases, and these were all located in the lung. Among all patients with gastrointestinal sarcomas, there was a 15% incidence of metastases to regional lymph nodes.

Survival

The 5-year survival rate for all patients with gastrointestinal sarcomas treated at MCV during the period of study was 40%. When the data were analyzed according to the extent of resection, it is clear that complete excision afforded the only hope for long-term survival. The 5-year survival rate for patients who had complete resection was 63%, as compared with 10% surviving at 5 years after partial excision ($p < 0.0001$). At 10 years the overall survival rate for patients having complete tumor resection was 48% (Fig. 1). The 5-year disease-free survival rate of patients having complete resection was 58%.

Various prognostic factors were analyzed to determine their effect on survival. Analysis of survival data based on grade of tumor revealed a significantly better 5-year survival rate of 75% for patients with Grade 1 tumors, as compared with 16% and 28% for Grade 2 and 3 tumors, respectively ($p = 0.0013$); there was no significant difference between Grades 2 and 3. The 10-year survival rate for Grade 1 tumors was 60% but was less than 10% for Grades 2 and 3 (Fig. 2). Those patients with tumors smaller than 10 cm had a significantly better 5-year survival rate of 78% as compared with 38% for those patients whose tumors were greater than or equal to 10 cm ($p = 0.03$) (Fig. 3). There was also a significant improvement in the 5-year survival rate (58%) in those patients whose tumors were confined to the site of origin when compared with patients whose tumors invaded adjacent organs (20%) ($p = 0.05$). There were no 5-year survivors among those patients who had distant metastases, and their median survival was only 10 months (Fig. 4). There were no statistically significant differences in terms of survival between sarcomas located in the stomach, small bowel, or colorectum. Other factors, such as sex of the patient or duration of symptoms, also did not correlate with survival.

Radiation and/or Chemotherapy

Of the 21 patients who had partial resection of their tumors, 12 (57%) also received therapeutic radiation

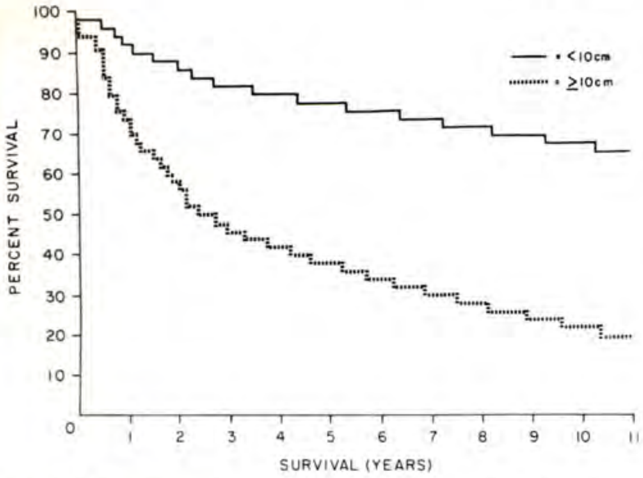

FIG. 3. Actuarial survival curves for all patients with primary gastrointestinal sarcomas based on size of the primary tumor.

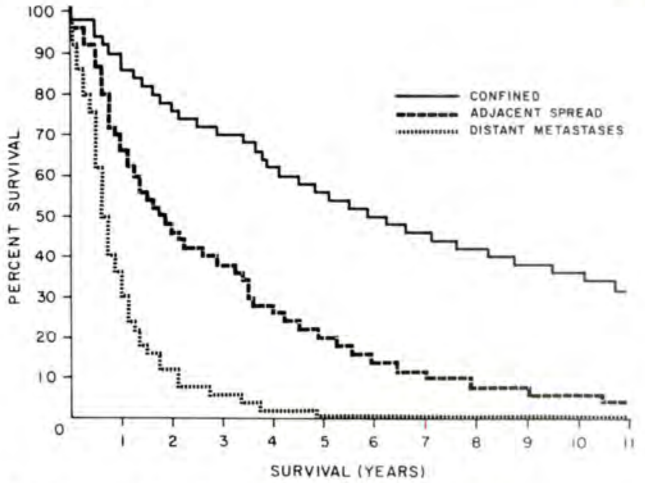

FIG. 4. Actuarial survival curves for all patients with primary gastrointestinal sarcomas based on extent of disease.

and/or chemotherapy; there was no difference in survival when compared with those patients who had operation alone (Table 5). The most frequently used chemotherapeutic regimen was doxorubicin HCl (Adriamycin®; Adria, Columbus, OH) and DTIC, alone or in combination with vincristine and cyclophosphamide. Total radiation doses ranged from 4500 to 5400 rads.

Discussion

Gastrointestinal sarcomas are uncommon malignant tumors that occur throughout the entire alimentary tract. The distribution of these tumors in our series is similar to the review of the 725 gastrointestinal leiomyosarcomas in the literature as of 1965, which reported the distribution as follows: esophagus 5%, stomach 47%, small bowel 35%, and colorectum 12%.[2] Because the alimentary tract has more smooth muscle than any other part of the body, it is not surprising that virtually all gastrointestinal sarcomas are leiomyosarcomas. The malignant fibrous histiocytoma of the appendix and the hemangiopericytoma of the colon in our series represent extremely rare cases.

The most frequent clinical presentations are abdominal pain, gastrointestinal bleeding, and/or an abdominal mass. Of note is that more than two-thirds of the patients that had gastrointestinal bleeding could have complete resection of their tumors, suggesting that small tumors causing early symptoms had a more favorable prognosis. In the past the diagnosis of gastrointestinal sarcomas was usually made at the time of a laparotomy, prompted by either radiologic studies with abnormal findings, intestinal obstruction, or gastrointestinal bleeding. With the advent of fiberoptic endoscopy, a tissue diagnosis may be made before operation for gastric and colorectal tumors, which could aid in pretreatment management decisions.

Surgical resection is the treatment of choice for gastrointestinal sarcomas, and appropriate surgical management requires every effort for complete excision of the tumor with an adequate margin of normal tissue. Resection of adjacent organs is often necessary to ensure complete excision. Several reviews have shown that small tumors (<5 cm) of the stomach can be adequately treated by wedge gastric resection with a generous margin of normal gastric wall.[5–7] Larger gastric sarcomas may require subtotal or total gastrectomy, and this should include omentectomy and resection of juxtagastric nodes. There is a discrepancy in the literature regarding the prevalance of nodal spread of gastrointestinal sarcomas, with some reports indicating little or no spread to regional lymph nodes[6–9] and others reporting a 10–15% incidence of nodal spread.[5,10–12] Our patients demonstrated a 15% incidence of spread to regional lymph nodes from all gastrointestinal sarcomas. The incidence of metastases to regional lymph nodes was only 6% for Grade 1 tumors as compared with 19% for Grade 2 tumors and 21% for Grade 3 tumors. Although it may not be necessary to include regional nodes in the resection of Grade 1 tumors, the grade of the tumor cannot be accurately assessed until the entire specimen is resected. Thus, because of this small but definite incidence of spread to regional nodes, and because including these nodes in the resection does not increase the morbidity

TABLE 5. *Results of Therapeutic Radiation (RT) or Chemotherapy (CT) on Survival of Patients with Gastrointestinal Sarcomas*

	Patients		Median Survival (Months)
	No.	(%)	
Partial resection	21		9
Surgery ± RT ± CT	12	(57)	9
Surgery alone	9	(43)	10

rate, we recommend a wide segmental resection with associated mesentery and/or omentum for all gastrointestinal sarcomas.

Reported survival data after operations for gastrointestinal sarcomas have been extremely variable, especially with respect to gastric sarcomas. The rates for curative resection for gastric sarcomas have ranged from 68 to 90%, with an overall 5-year survival rate between 19% and 56% and a 5-year survival rate after curative resection ranging from 32 to 63%.[6,7,10,13,14] Reports on sarcomas of the small and large intestine have been more consistent with 5-year survival figures of between 40% and 50% for all patients and those receiving complete excision.[9,15-17] This review reports a 5-year survival rate of 40% for all patients with gastrointestinal sarcomas and 63% for those able to have complete excision of their tumors. There was no significant difference in survival rate between sarcomas located in the stomach as compared with those in the small or large intestine.

Several prognostic factors were analyzed to determine their effect on survival, and the most significant factor affecting survival was the histologic grade of sarcoma. The method of grading sarcomas in this review was similar to that initially described for soft tissue sarcomas[18,19] and that recently reported for use with gastrointestinal sarcomas.[6,7,20] Grading was determined by a composite observation of the mitotic rate, degree of atypia or anaplasia, degree of cellularity, and degree of differentiation. The mitotic count appears to be the most objective and reproducible feature when determining the grade of malignancy; however, as noted by Appelman and Helwig, this needs to be related to the histologic appearance of the tumor.[5] More recently, Appelman has tended to downgrade the value of using mitotic counts in evaluating malignancy in stromal tumors of the gut. He found that the site of the primary tumor may be more valuable in tumor behavior prediction than a set number of mitotic counts.[21,22] Nevertheless, our results show that once the diagnosis of sarcoma is established, no difference in survival occurred on the basis of tumor location. This review clearly demonstrates that low-grade sarcomas (Grade 1) had a much better prognosis than higher grade sarcomas (Grades 2 and 3). This observation is related to the fact that nearly all (88%) Grade 1 sarcomas could be completely excised and, of those, only 14% eventually had metastases develop, whereas only 35% of Grade 3 sarcomas could be resected for cure and for half of those metastatic disease eventually developed. Other factors that were associated with a better prognosis were smaller tumors (<10 cm) and tumors confined to the site of origin, as noted in previous reports.[7,10,16]

Our study demonstrated no benefit from therapeutic radiation and/or chemotherapy; however, the number of patients treated was small and the role of radiation or chemotherapy cannot be adequately assessed with so few cases. Review of the literature has also failed to reveal a significant benefit from these nonsurgical modalities in an adjuvant or therapeutic setting.[6,7,15] However, the 42% recurrence rate in patients with curative resection in this review and reports that up to 78% of patients will eventually have distant metastases develop[5,6,20] warrant further investigation into the role of adjuvant therapy.

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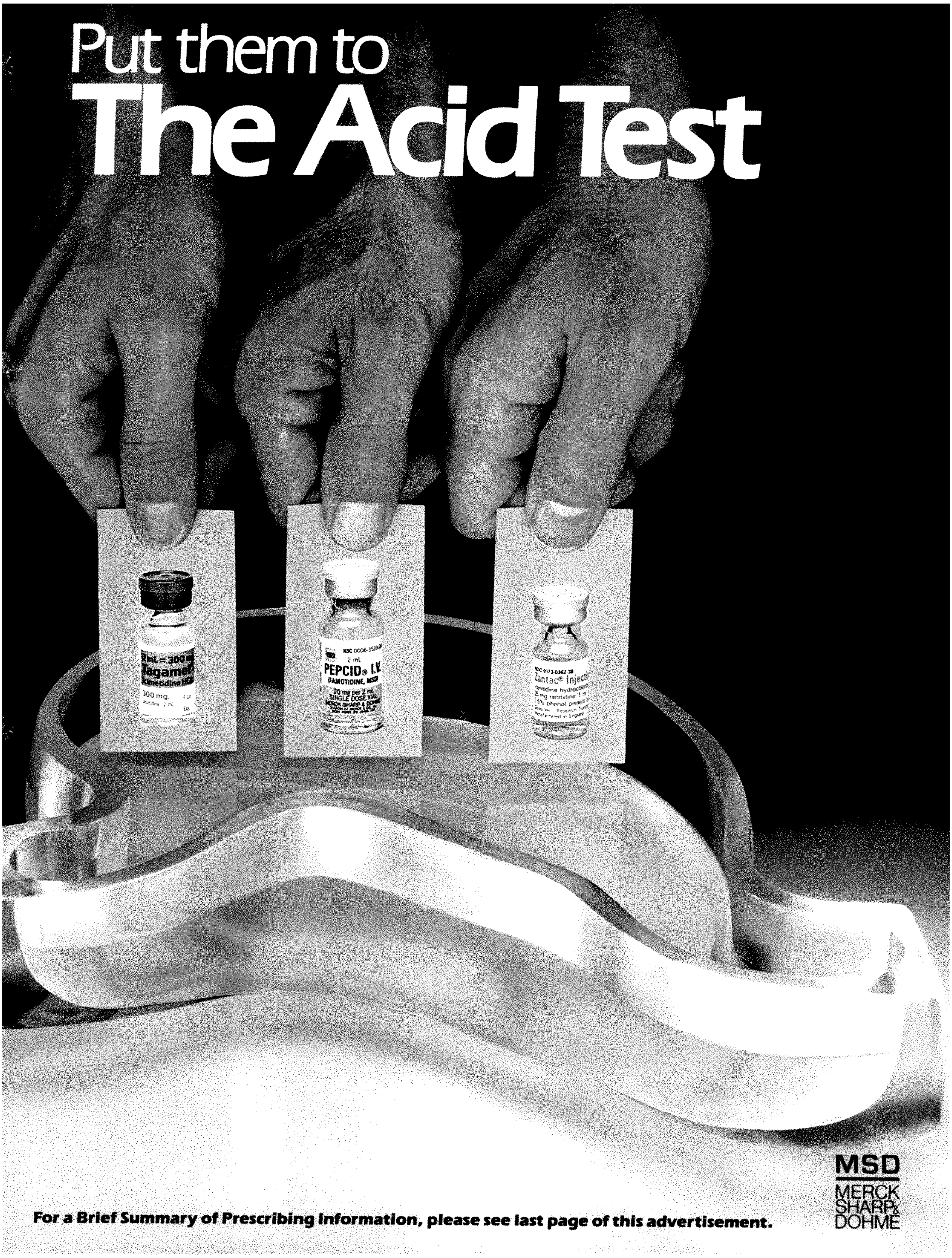

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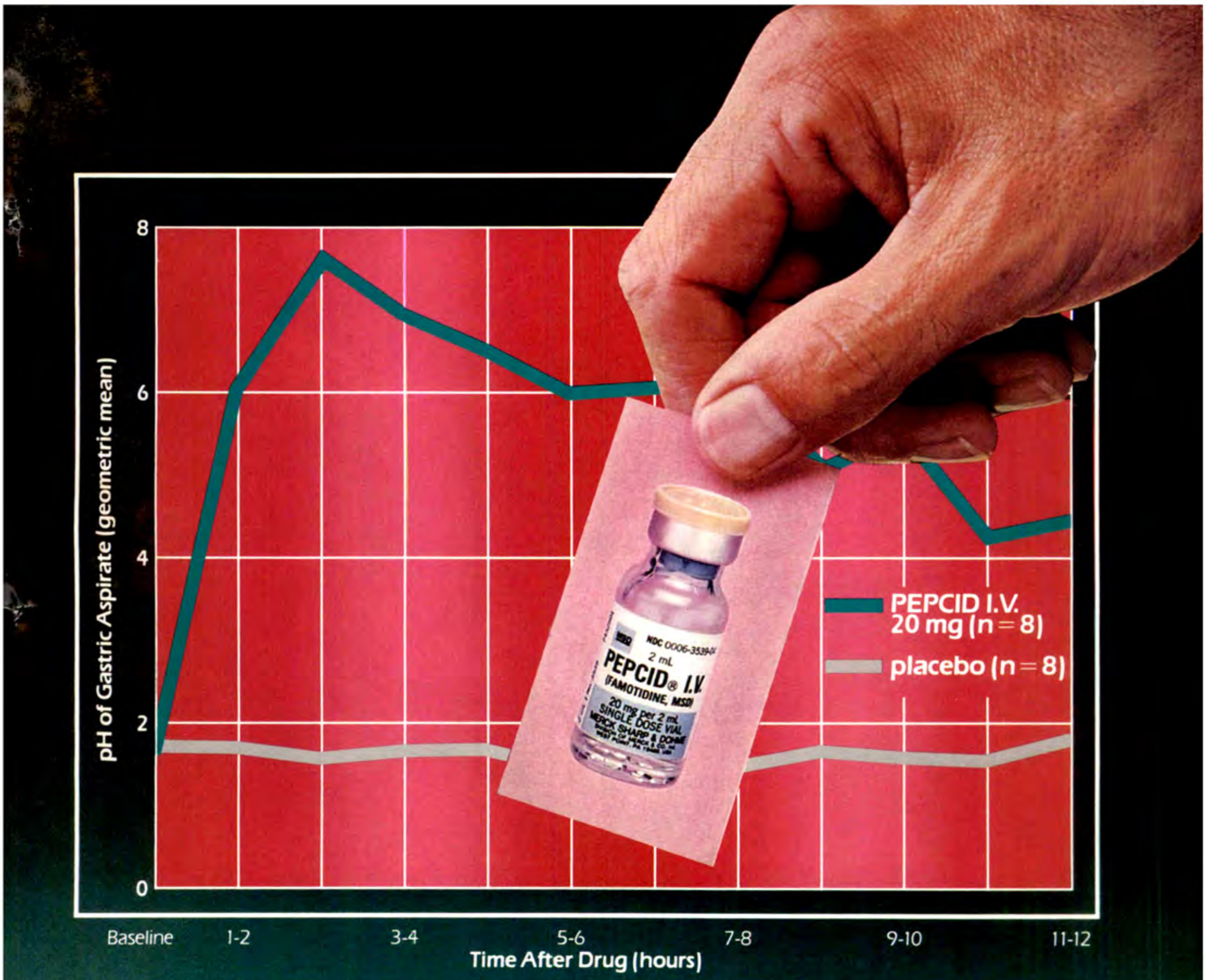

A double-blind, placebo-controlled study[1] involving eight volunteer hypersecretor subjects. The pH of gastric aspirates was measured hourly for 12 hours following single intravenous doses. PEPCID I.V. maintained the mean gastric pH above 4.0 at all time points throughout the 12-hour period with one 20-mg I.V. dose.

[1] Ryan, J.R. et al.: Comparison of effects of oral and intravenous famotidine on inhibition of nocturnal gastric acid secretion, Am. J. Med. 81 (Suppl. 4B): 60-64, October 24, 1986.

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Right Lower Quadrant Pain in Young Patients with Leukemia

A Surgical Perspective

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A retrospective review of cecal and appendiceal complications occurring in young patients with acute leukemia since 1969 was performed. The objective of this study was to determine the relative incidence of appendicitis and typhlitis among patients with acute leukemia who had operation or autopsy in this institution as well as to determine the risks of operative intervention. Fifteen patients with these complications were identified among the 400 patients with acute leukemia seen during this time period. Signs and symptoms of an acute abdomen were present despite immunosuppression. The incidence of sepsis at the time of presentation was 53%. Preoperative risk factors identified most frequently were coagulopathy and organ failure resulting from sepsis. Postoperative morbidity (25%) and mortality rates (8%) were related to the development of infectious complications. Appendicitis occurred in eight of the 15 patients studied, whereas typhlitis or its complications was found in seven patients. No preoperative factors could be found to differentiate typhlitis from appendicitis on clinical examination. It is suggested that operation can be safely performed in neutropenic patients who have acute right lower quadrant pain and signs of peritoneal irritation and may be the only effective way of differentiating appendicitis from typhlitis.

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INCREASINGLY AGGRESSIVE CHEMOTHERAPEUTIC REGIMENS have brought about improved long-term survival rates of up to 60% in patients with acute lymphocytic leukemia.[1,2] These aggressive regimens expose the patients to complications and death related to bone marrow suppression and neutropenia with the attendant infectious complications. The mortality rate from gram-negative sepsis approaches 40%. In patients with polymicrobial sepsis with cancer, the mortality rate is 70%.[3]

Intra-abdominal and, specifically, right lower quadrant (RLQ) infectious complications often are the source of such sepsis.[4] The evaluation and treatment of these intra-abdominal infectious complications involve the surgeon. Evaluation is often difficult in these critically ill immunosuppressed patients. The otherwise straightforward evaluation of RLQ pain in a young patient is obscured by the patient's underlying disease or treatment.[5] The range of pathologic processes to be expected and the implications of signs and symptoms in these patients might differ from those of "normal" patients, therefore making clinical assessment difficult for the surgical consultant. Consideration of the risks of operation in such patients adds to the difficulty in management.[4-6]

We have reviewed our experience with RLQ complications in young patients having chemotherapy for leukemia in order to determine the incidence of typhlitis and appendicitis, relative to each other, and to assess the risks of operative intervention. We have also attempted to document the incidence of localized and diffuse abdominal pain exhibited by this group of patients. Additional diagnoses made in relation to abdominal pain were documented, as well as the incidence of laparotomies with normal findings.

Methods

Discharge diagnoses at the Clinical Center, National Institutes of Health (NIH), between 1969 and 1984 identified 400 patients admitted for acute leukemia (AL) that were between the ages of 3 and 21 years. Of this group of 400 patients, 129 sustained 135 episodes of documented abdominal pain. The diagnoses related to these episodes were based on clinical laboratory, radiologic, and/or pathologic results recorded in these charts. Ninety-six of these 129 patients had autopsies at this institution available for analysis. Sixteen of the patients

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TABLE 1. *Leukemic Patients with Right Lower Quadrant Complications*

		Age	
	N	Range	(Median)
Group 1 (operation)	13	5–12	(12)
Group 2 (autopsy)	3	7, 10, 21	(10)

had RLQ pathologic conditions identified as cecitis, typhlitis, appendicitis, cecal or appendiceal perforation, and mesenteric adenitis. The records of these 16 patients were then reviewed for the status of the primary disease, initial symptoms and signs with the RLQ complications, hematologic values, radiologic findings, and initial microbiologic results with abdominal signs or symptoms. Charts were also examined to determine the drug therapy preceding this complication. Operative risk factors, defined as hemodynamic instability, coagulopathy, or respiratory failure, were evaluated. Indications for operation, operation performed, and operative findings, as well as operative complications and deaths, were recorded. The results reported in surgical pathology (13 patients) and autopsy reports (three patients) were evaluated. Minimum follow-up period was 14 months. Additional causes of abdominal pain documented in 113 patients were also recorded.

Results

Study Group

Of the 400 patients admitted with AL who were between the ages of 3 and 21 years, 129 (32%) had a total of 135 documented episodes of abdominal pain. Among the 129 patients, 16 (12%) had laparotomies for RLQ findings (Table 1). Thirteen patients had operation (group 1), and three (group 2) patients had their disease confirmed at autopsy. Ages were from 3 to 21 in the leukemic patients. Nine were male patients and seven were female patients. Eleven patients had acute myelogenous leukemia, and six had acute lymphocytic leukemia.

Eleven of the 16 patients with AL with RLQ findings had evidence of advanced disease, including positive bone marrow aspirate findings or evidence of visceral involvement. Seven patients were seen during initial induction chemotherapy, six during re-induction therapy for relapse, and two while their disease was in remission. Median survival for patients operated on was 7 months after surgery (range: 1 week to 5 years). All patients studied at autopsy died within 1 month of presentation with RLQ symptoms or signs.

Clinical Findings

A total of 125 patients studied had documented abdominal pain. Among the 135 episodes of AL, 60 were localized and 75 were diffuse. In 11 of 16 patients with AL with cecal or appendiceal pathologic conditions, the pain was localized to the RLQ of the abdomen, whereas four others had diffuse abdominal pain. Thirteen of 16 patients had fever and chills, whereas 10 had nausea and vomiting. All operated patients had abdominal tenderness to palpation that was localized to the RLQ. Thirteen of the 16 had documented peritoneal signs (rebound, abdominal wall rigidity, or involuntary guarding). All patients operated on had peritoneal signs. In 14 of the 16 operated leukemic patients, their temperatures were greater than 39 C for 2 consecutive days. One patient with AL had a palpable RLQ mass documented.

Laboratory and Radiologic Findings

Eight of the 16 patients with AL had leukocyte counts less than 2,000/mL, and four had counts between 2,000 and 10,000/mL. Three counts were greater than 15,000/mL. Ten of the 15 patients with AL were at their nadir leukocyte count at the time of their presentation. In 10 of the patients with AL the platelet counts were less than 70,000/mL (Table 2).

In two patients with AL intraperitoneal free air was seen on chest roentgenograph. Nine of 15 patients had abdominal roentgenographs showing dilated small bowel or air fluid levels.

Eight young patients with leukemia had positive blood culture results, despite the use of multiple prophylactic or empiric antibiotics in 14 of the patients. Six patients had gram-negative organisms cultured from their blood, one patient had anaerobic sepsis, and one

TABLE 2. *Hematologic Status*

		WBC Count				
	N	<2000	2000–10,000	>15,000	At Nadir	Platelet Count <70,000
Group 1	13	6	4*	3*	7	7
Group 2	3	2	1*	0	3	3

* Abnormal cells seen in smear of these patients.

TABLE 3. *Microbiology*

	N	Positive Blood Culture	Receiving Antibiotic Therapy
Group 1	13	5* (44%)	10
Group 2	3	3* (100%)	3

* Six of eight gram-negative enteric bacteria.

patient had polymicrobial sepsis, including fungemia (Table 3).

Only one of the patients with AL was not receiving or had not recently received antineoplastic therapy at the time of presentation. Five of these patients were being treated with chemotherapy at the time of complication, whereas nine patients had received chemotherapy within the preceeding 20 days. Eight patients with AL had received steroids within 15 days.

Operative Risk Factors

In a retrospective assessment of the operative risk factors at presentation of patients with AL, 10 patients had a coagulopathy (protime, plasma thromboplastin time > control and/or platelet count < 70,000), four had hemodynamic instability (defined as hypotension [blood pressure < 90] and requiring treatment with the volume expansion and/or vasopressors), and one was in respiratory failure. Of the 13 patients with AL operated on, indications for operation included acute abdominal pain with peritoneal signs in 11 and a suspected intra-abdominal abscess in one. A total of fourteen laparotomies were performed in 13 patients with AL. Nine had simple appendectomies, two had appendectomies with drainages of abscesses, and two had right hemicolectomies. At operation six patients had simple appendicitis, two had perforated appendices, two had cecal perforation, two had evidence of localized abscess formation, and one had a diagnosis of mesenteric adenitis. In the 13 leukemic patients operated on, there was one death resulting from overwhelming continued sepsis. There was one re-operation for cecal perforation in a patient after appendectomy. There were three wound infections, three cases of intra-abdominal sepsis, a single case of respiratory failure, and one wound dehiscence. All of these complications occurred among three patients. The leukemic patients for whom autopsies were performed all died with sepsis 2–14 days after the onset of symptoms (Table 4).

TABLE 4. *Operative Deaths and Complications (Group 1)*

	Number of Patients
Wound infection	3
Intra-abdominal sepsis	3
Respiratory failure	1
Wound dehisence	1
Reoperation	1
Death	1
Total	13

TABLE 5. *Pathologic Condition at Operation or Autopsy in Patients with Right Lower Quadrant Symptoms*

	N	Appendicitis	Typhlitis	Mesenteric Adenitis
Group 1	13	8	4	1
Group 2	3	0	3	0

Pathologic Findings

Pathologic examination at either operation or autopsy revealed eight cases of appendicitis (two of these with leukemic infiltrates and one with an associated abscess) among the leukemic patients. Two had normal appendices with cecal edema, and five had cecal necrosis (two with associated intra-abdominal abscesses) consistent with typhlitis. One had mesenteric adenitis documented by culture and biopsy (Table 5).

Additional Causes of Abdominal Pain in Leukemic Patients

Of the 129 young patients with acute leukemias, there were 135 documented episodes of abdominal pain; 60 were localized and 75 were diffuse. Aside from the patients with RLQ findings previously described, the clinical or pathologic diagnosis assigned to the cause of the abdominal pain was varied (Table 6). These were based on clinical, laboratory, radiologic, or pathologic findings recorded in the medical records. Autopsies were done on 92 of these 129 patients at this institution.

TABLE 6. *Other Causes of Abdominal Pain in Young Patients with Acute Leukemia*

Cause	N
Drug-induced illeus or enteritis	6
Pancreatitis	17
Perforated viscus (other than cecum)	10
Parasite infestation	3
Graft *vs.* host disease	2
Pelvic inflammatory disease	2
Cholecystitis	2
Splenic rupture or abscess	3
Bowel obstruction resulting from leukemic infiltrates	2
Intussuception	2
No diagnosis given	9

Discussion

The purpose of this study was to determine the relative incidence of appendicitis and typhlitis among young leukemic patients at our institution. The incidence of appendicitis and typhlitis lesions among young leukemic patients was roughly equal in a review of operated or autopsied patients. In 400 patients seen over a period of 15 years at the NIH, acute appendicitis was identified in eight and cecal edema, necrosis, or perforation consistent with typhlitis was noted in seven. One had a laparotomy with normal findings with the diagnosis of mesenteric adenitis by biopsy and culture. Cecal edema alone was found in two of the eight patients with typhlitis. The true incidence of these lesions in this population probably is higher because of the presence of less severe cases of typhlitis that do not come to operation or autopsy. The estimated incidence of clinically significant and pathologically proven cecal and appendiceal complications has been determined in this study to be at least 4% among all leukemic patients between the ages of 3 and 21 years. Among patients with AL to be operated on who had RLQ pain, appendicitis or typhlitis can be expected with equal frequency and will be found in 26% of those with localized RLQ pain.

Leukemic patients who presented with significant RLQ symptoms had sufficient indications for operation and had signs of peritoneal irritation documented despite having advanced disease or having received chemotherapy or steroids. All patients in our study had significant fever. These RLQ complications produced the clinical picture of an acute abdomen. Thirteen of 15 patients who had these problems did so during induction therapy for their leukemia. The low incidence of laparotomies with normal results in this group of patients probably reflects their perceived high operative morbidity and mortality rates.

Many of these patients appeared to be poor operative risks because of coagulopathy and hemodynamic instability. The incidence of sepsis in these young leukemic patients was high (53%) and usually resulted from gram-negative organisms. This occurred despite the liberal use of antibiotics. One-third of the leukemic patients demonstrated signs of major organ failure related to their sepsis.

The most common reported cause of death in leukemic patients is from sepsis.[8] In a study of 89 cases of perforated appendicitis at Los Angeles Children's Hospital, only 6% of blood cultures had positive results compared with 53% of our young leukemic patients.[9] Septicemia in patients with leukemia has been reported to result in a 20–40% mortality rate.[8] Studies of leukemic patients with surgical complications have demonstrated the incidence of sepsis to be as high as 75%.[4] Appendicitis and typhlitis, or their complications, appear to be associated with significant morbidity and mortality rates in leukemic patients.

The term typhlitis in this setting was first used by Wagner et al. in 1970.[10] It referred to a necrotizing colitis involving the cecum or the cecum and appendix and was found in leukemic children who were receiving therapy and were often in the terminal stages of their disease. Others have used the term neutropenic enteropathy or referred to these clinical pictures as the ileocecal syndrome.[7,11] In autopsy series, the incidence of these lesions ranges from 9.9 to 12%. Both appendiceal and cecal complications have been estimated as occurring with an incidence of approximately 5%.[4,12,13] Although occurring infrequently, appendicitis is associated with a high mortality rate in leukemic patients.[13–15]

The vaguely defined clinical diagnosis of typhlitis is difficult, and operative findings range from simple edema of the cecum to a frankly necrotic and perforated cecum.[10,12,13,16] Diagnosis of this disorder without pathologic examination is speculative and the differentiation from appendicitis is unclear.[17] The role of surgical management in appendicitis is clear. The role of surgical therapy in typhlitis is less well defined.[15,18,19] Recommendations for therapy range from nonoperative therapy to right hemicolectomy.[20–24] Pleas for nonoperative therapy are often based on the patient's poor outlook for survival because of his or her underlying disease, a fear of surgical complications, or even hopes that the patient will be able to localize a cecal perforation.[25,26] Although conservative therapy can be successful in some instances of typhlitis, there are no prognostic signs that differentiate it from appendicitis or that predict progression to cecal necrosis. A review of 65 cases of appendiceal and cecal complications in young (<30 years) patients with ALL reported in the medical literature in 13 articles show only two nonoperative survivors. Of 26 operated patients, there were 21 who survived for more than 30 days (Table 7). A well-described syndrome of cecal necrosis or perforation in immunosuppressed patients receiving therapy with steroids or chemotherapy can also occur.[27,28]

In our patients, appendectomy was performed with minimal complications. Progression of the appendicitis to perforation or abscess formation puts the patient at high risk for subsequent infectious complications, illness, and death. Despite the poor preoperative risk status of these patients in terms of coagulopathy and associated organ failure, most of the complications seen in the operated patients were thought to be directly related to the patients' susceptibility to infection. The risk to the patient from surgically treatable intra-abdominal sepsis appears greater than the risk of complications from the surgical exploration in this setting. We are in

TABLE 7. *Outcome of Surgical and Nonsurgical Therapy for Young Leukemic Patients with Appendicitis and Typlitis: Review of the Literature*

Institution	Operated Cases	Operated Survivors	Nonoperative Cases	Nonoperative Survivors (>30 Days)
University of Chicago[12]	1	0	7	0
Long Island Jewish Medical Center[28]	1	1	—	—
Childrens Medical Center, Seattle[17]	4	3	—	—
Walter Reed General Hospital[29]	—	—	1	0
Memorial Sloan-Kettering[5]	1	1	2	0
Childrens Hospital of Los Angeles[7]	3	2	8	0
Hadassah University Hospital[26]	—	—	1	0
Columbia-Presbyterian Medical Center[16]	4	3	1	1
Memorial Sloan-Kettering[25]	—	—	1	1
Childrens Hospital of Los Angeles[13]	3	3	7	0
Memorial Sloan-Kettering[4]	6	5	6	0
Brooke Army Medical Center[22]	2	2	—	—
St. Jude Hospital[18]	1	1	5	0
Total	26	21 (78%)	39	2 (5%)

agreement with Schaller, who noted "that the sickest patients are the ones about whom the surgeon tends to procrastinate yet they are also the patients who may benefit most from early operation."[29]

Our study cannot address the larger questions of the outcome of abdominal pain in the great number of neutropenic patients with cancer who did not come to operation or autopsy who may have these disorders in milder forms. The relative efficacy of operative and nonoperative therapy on outcome of these patients can only be addressed in a prospective evaluation of these patients. In our leukemic patients operated on, median postoperative survival was significant (7 months), thus allowing the patient's survival to be determined by his response to chemotherapy. We are initiating a prospective evaluation of neutropenic patients with abdominal pain that will attempt to determine factors relevant to outcome.

Documented abdominal pain occurred in 32% of the young leukemic patients seen during the study period. Of the 135 episodes, 60 were localized and 75 were diffuse. When the clinical diagnosis of the cause for abdominal pain is evaluated, it can be seen that most of such episodes will respond to supportive cause and do not require operation.

Typhlitis and appendicitis appear to be equally common in the young leukemic patient with RLQ signs of peritoneal irritation. The preoperative differentiation between these two problems is difficult, and one cannot be secure in recommending nonoperative treatment. The classical signs of peritoneal irritation can be found in these patients despite their neutropenia and immunosuppressed condition and have the same implications as in the nonleukemic patient. The greatest risk to these patients appears to be from progressive local and systemic infection. This series and review of the literature suggests that appropriate surgical treatment in terms of drainage of purulent material and appropriate resection of compromised tissues should strongly be considered in young leukemic patients with these findings.

Summary

In this review of leukemic patients admitted at the NIH over a period of 15 years with cecal and appendiceal complications, we find that appendicitis and typhlitis ranging from cecal edema to necrosis were equal in incidence among patients with signs of RLQ peritoneal irritation. Despite substantial preoperative risk factors, including coagulopathy and organ failure, operation could be performed safely with adequate supportive measures. Sepsis was common at the time of presentation, occurring in 53% of our patients. There were no discernable factors that differentiated appendicitis from typhlitis before operation or before autopsy. Operative death and complications were related to the patients' susceptibility to infection. We believe that neutropenic patients presenting with RLQ findings of peritoneal irritation can be operated on safely. In addition, this may be the only effective way to differentiate appendicitis from typhlitis.

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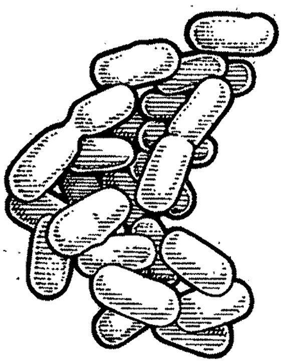

*Percent susceptible at 16 mcg/mL: *B. fragilis* (91%), *B. thetaiotaomicron* (84%), *B. distasonis* (78%), *B. vulgatus* (88%), and *B. ovatus* (79%). Based on Antibiotic Susceptibility Reports, National Summary, in *The Bacteriologic Report: Volume I 1987*, Totowa, NJ, BAC-DATA® Medical Information Systems, Inc., 1987.

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MEFOXIN® (Cefoxitin Sodium, MSD) is indicated for the treatment of intraabdominal, gynecological, lower respiratory tract, and skin and skin-structure infections due to designated susceptible organisms including members of the *Bacteroides fragilis* group. (See Brief Summary for complete listing of Indications.)

MEFOXIN is contraindicated in patients who have shown hypersensitivity to cefoxitin and the cephalosporin group of antibiotics. Before therapy with MEFOXIN is instituted, careful inquiry should be made to determine whether the patient has had previous hypersensitivity reactions to cefoxitin, cephalosporins, penicillins, or other drugs. This product should be given with caution to penicillin-sensitive patients.

Pseudomembranous colitis, from mild to life-threatening in severity, has been reported with virtually all antibiotics (including cephalosporins); therefore, it is important to consider its diagnosis when diarrhea develops in association with antibiotic use.

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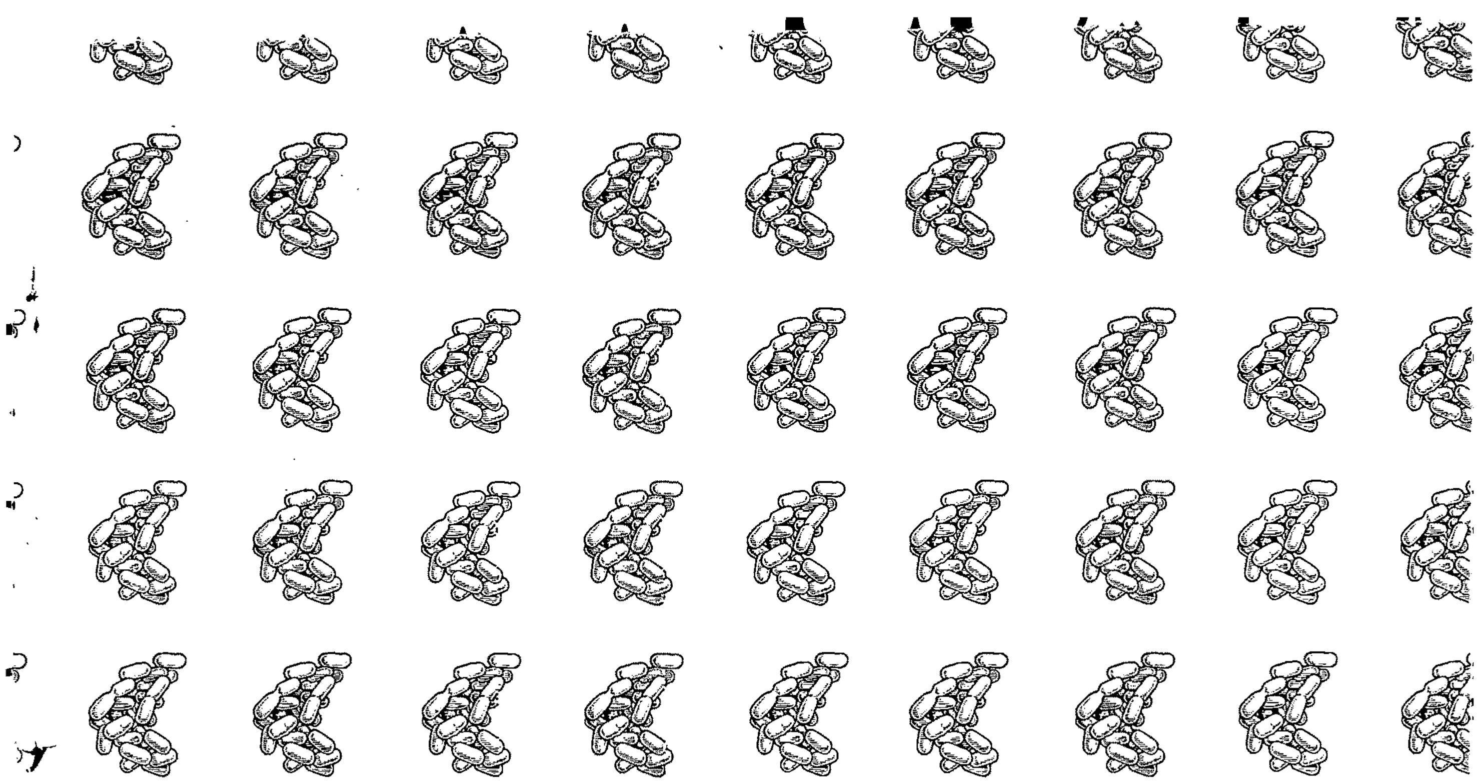

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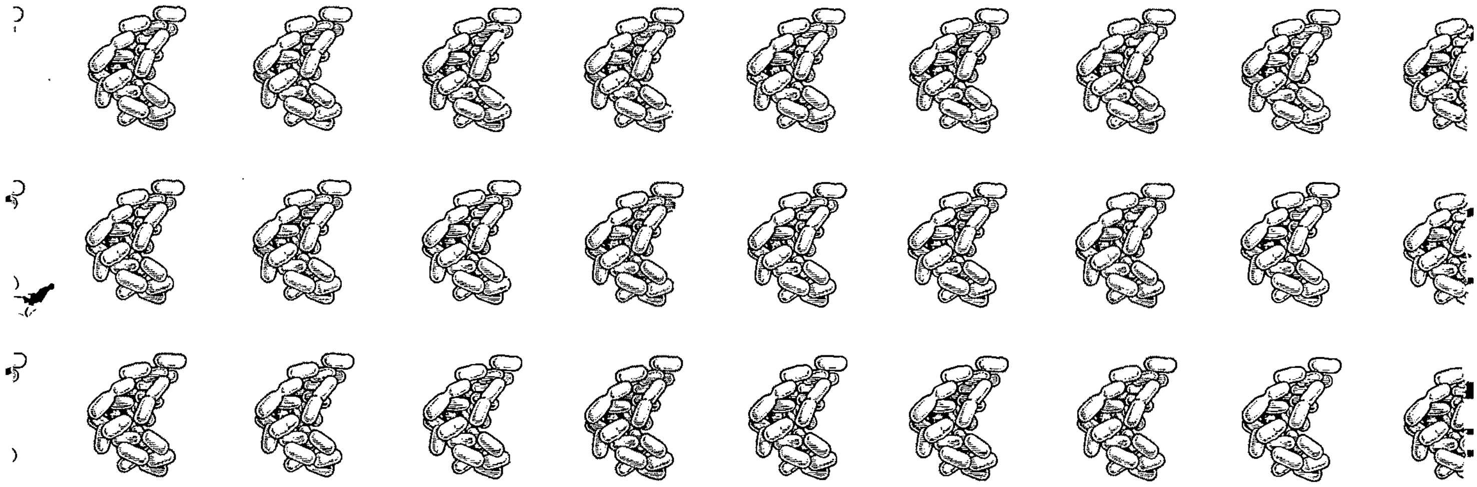

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Indications and Usage: *Treatment*—Serious infections caused by susceptible strains of the designated microorganisms in the following diseases:

LOWER RESPIRATORY TRACT INFECTIONS, including pneumonia and lung abscess, caused by *Streptococcus pneumoniae* (formerly *Diplococcus pneumoniae*), other streptococci (excluding enterococci, e.g., *Strep. faecalis*), *Staphylococcus aureus* (penicillinase and non-penicillinase producing), *Escherichia coli*, *Klebsiella* species, *Hemophilus influenzae*, and *Bacteroides* species.

GENITOURINARY INFECTIONS. Urinary tract infections caused by *E. coli*, *Klebsiella* species, *Proteus mirabilis*, indole-positive *Proteus* (i.e., *P. morganii*, *P. rettgeri*, and *P. vulgaris*), and *Providencia* species. Uncomplicated gonorrhea due to *Neisseria gonorrhoeae* (penicillinase and non-penicillinase producing).

INTRA-ABDOMINAL INFECTIONS, including peritonitis and intra-abdominal abscess, caused by *E. coli*, *Klebsiella* species, *Bacteroides* species including the *B. fragilis* group,§ and *Clostridium* species.

GYNECOLOGICAL INFECTIONS, including endometritis, pelvic cellulitis, and pelvic inflammatory disease, caused by *E. coli*, *N. gonorrhoeae* (penicillinase and non-penicillinase producing), *Bacteroides* species including the *B. fragilis* group,§ *Clostridium* species, *Peptococcus* species, *Peptostreptococcus* species, and group B streptococci.

SEPTICEMIA caused by *Strep. pneumoniae* (formerly *D. pneumoniae*), *Staph. aureus* (penicillinase and non-penicillinase producing), *E. coli*, *Klebsiella* species, and *Bacteroides* species including the *B. fragilis* group.§

BONE AND JOINT INFECTIONS caused by *Staph. aureus* (penicillinase and non-penicillinase producing).

SKIN AND SKIN STRUCTURE INFECTIONS caused by *Staph. aureus* (penicillinase and non-penicillinase producing), *Staph. epidermidis*, streptococci (excluding enterococci, e.g., *Strep. faecalis*), *E. coli*, *P. mirabilis*, *Klebsiella* species, *Bacteroides* species including the *B. fragilis* group,§ *Clostridium* species, *Peptococcus* species, and *Peptostreptococcus* species.

Although appropriate culture and susceptibility studies should be performed, therapy may be started while awaiting these results. Cefoxitin is not active *in vitro* against most strains of *Pseudomonas aeruginosa* and enterococci (e.g., *Strep. faecalis*) and many strains of *Enterobacter cloacae*. Methicillin-resistant staphylococci are almost uniformly resistant to cefoxitin.

Contraindications: Previous hypersensitivity to cefoxitin and the cephalosporin group of antibiotics.

Warnings: BEFORE THERAPY IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE PREVIOUS HYPERSENSITIVITY REACTIONS TO CEFOXITIN, CEPHALOSPORINS, PENICILLINS, OR OTHER DRUGS. GIVE WITH CAUTION TO PENICILLIN-SENSITIVE PATIENTS. ANTIBIOTICS SHOULD BE ADMINISTERED WITH CAUTION TO ANY PATIENT WHO HAS DEMONSTRATED SOME FORM OF ALLERGY, PARTICULARLY TO DRUGS. IF AN ALLERGIC REACTION TO CEFOXITIN OCCURS, DISCONTINUE THE DRUG. SERIOUS HYPERSENSITIVITY REACTIONS MAY REQUIRE EPINEPHRINE AND OTHER EMERGENCY MEASURES.

Pseudomembranous colitis, from mild to life-threatening in severity, has been reported with virtually all antibiotics (including cephalosporins); therefore, it is important to consider its diagnosis when diarrhea develops in association with antibiotic use. Broad-spectrum antibiotics alter normal flora of colon and may permit overgrowth of clostridia; a toxin produced by *Clostridium difficile* is a primary cause of antibiotic-associated colitis. Mild cases may respond to drug discontinuance alone; in more severe cases, management may include sigmoidoscopy, appropriate bacteriological studies, fluid, electrolyte and protein supplementation, and use of a drug such as oral vancomycin; isolation of the patient may be advisable. Other causes of colitis should also be considered.

Precautions: *General*—Total daily dose should be reduced in patients with reduced urinary output due to renal insufficiency because high and prolonged serum antibiotic concentrations can occur from usual doses. Prescribe with caution in patients with a history of gastrointestinal disease, particularly colitis. Prolonged use may result in overgrowth of nonsusceptible organisms; repeated evaluation of the patient's condition is essential. If superinfection occurs, take appropriate measures.

Drug Interactions—Increased nephrotoxicity has been reported following concomitant administration of cephalosporins and aminoglycoside antibiotics.

Drug/Laboratory Test Interactions—High concentrations (>100 mcg/mL) may interfere with measurement of serum and urine creatinine levels by the Jaffé reaction and produce false increases of modest degree in creatinine levels reported; serum samples should not be analyzed for creatinine if withdrawn within 2 hours of cefoxitin administration. High concentrations may interfere with measurement of urinary 17-hydroxy-corticosteroids by the Porter-Silber reaction and produce false increases of modest degree in levels reported. A false-positive reaction for glucose in urine has been observed with CLINITEST|| reagent tablets.

Carcinogenesis, Mutagenesis, Fertility Impairment—No long-term animal study has been performed on carcinogenic or mutagenic potential. Rat studies at approximately three times maximum recommended human dosage revealed no effects on fertility or mating ability.

Pregnancy Category B—Reproduction studies in rats and mice did not reveal teratogenic or fetal toxic effects, although fetal weights were slightly decreased. In rabbits, cefoxitin was associated with a high incidence of abortion and maternal death, neither considered teratogenic. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers—Excreted in human milk: Exercise caution.

Pediatric Use—Safety and efficacy in infants from birth to three months have not yet been established. In children three months and older, higher doses have been associated with increased incidence of eosinophilia and elevated SGOT.

Adverse Reactions: The most common adverse reactions have been local reactions following intravenous or intramuscular injection. Other adverse reactions have been encountered infrequently. *Local Reactions*—Thrombophlebitis with intravenous administration; pain, induration, and tenderness after intramuscular injections. *Allergic Reactions*—Rash (including exfoliative dermatitis), pruritus, eosinophilia, fever, and other allergic reactions including anaphylaxis. *Cardiovascular*—Hypotension. *Gastrointestinal*—Diarrhea, including documented pseudomembranous colitis during or after treatment, and, rarely, nausea and vomiting. *Blood*—Eosinophilia, leukopenia including granulocytopenia, neutropenia, anemia, including hemolytic anemia, thrombocytopenia, and bone marrow depression. A positive direct Coombs test may develop in some individuals, especially those with azotemia. *Liver Function*—Transient elevations in SGOT, SGPT, serum LDH, and serum alkaline phosphatase. *Renal Function*—Elevations in serum creatinine and/or blood urea nitrogen levels and, rarely, acute renal failure.

Note: In group A beta-hemolytic streptococcal infections, therapy should be maintained for at least 10 days to guard against the risk of rheumatic fever or glomerulonephritis. In staphylococcal and other infections involving a collection of pus, surgical drainage should be carried out where indicated. Intramuscular injections should be well within the body of a relatively large muscle such as the upper outer quadrant of the buttock (i.e., gluteus maximus); aspiration is necessary to avoid inadvertent injection into a blood vessel. The total daily dosage in infants and children should not exceed 12 grams.

How Supplied: Sterile cefoxitin sodium in vials, infusion bottles, and ADD-Vantage# vials containing 1 gram or 2 grams cefoxitin equivalent and in 10-gram bulk bottles.

§ *B. fragilis, B. distasonis, B. ovatus, B. thetaiotaomicron, B. vulgatus*

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For asymptomatic persons the Society recommends annual digital rectal examination at age 40 and over; at age 50 and over, an annual stool blood test, as well as sigmoidoscopy every three to five years, following two initial annual negative sigmoidoscopies.

We're here to help. You can reach us at your local American Cancer Society office or write to our Professional Education Department at National Headquarters, 90 Park Avenue, New York, N.Y. 10016. Ask about the Society's Colorectal Check program of professional and public education for the early detection of colorectal cancer.

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*"Cancer of the Colon and Rectum: Summary of Public Attitude Survey," *Ca* 33:359-365, 1983 (Nov.-Dec.).

Exocrine and Endocrine Stomach after Gastrobulbar Preserving Pancreatoduodenectomy

HWI-CHA KIM, M.D., TAKASHI SUZUKI, M.D., TAKEHIRO KAJIWARA, M.D.,* TAKASHI MIYASHITA, M.D.,
MASAYUKI IMAMURA, M.D., and TAKAYOSHI TOBE, M.D.

Exocrine and endocrine stomach was studied serially in 13 patients who had gastrobulbar preserving pancreatoduodenectomy (GPPD). In most of them, acid output temporarily increased just after operation but recovered. Gastrin response level decreased transiently but returned to the preoperative level. A negative correlation was observed between the acid and gastrin levels, which suggests that the negative feedback mechanism between parietal cells and G cells was maintained. Acid and gastrin levels in GPPD were higher than those in conventional pancreatoduodenectomy (cPD) but not remarkably different from those of the controls. No peptic ulcer was detected after the operation. These findings indicated that GPPD poses little problem concerning offensive factors. Postoperative ulcer formation is considered to be prevented by the authors' procedure, which is devised to best preserve defensive mechanisms so that duodenectomy is minimized and the gastrointestinal continuity is reconstructed physiologically from mouth to anus by end-to-end duodenoduodenestomy, end-to-side pancreatojejunostomy, and end-to-side choledochojejunostomy.

*From the First Department of Surgery, Faculty of Medicine, Kyoto University, Kyoto, Japan, and the Department of Surgery, Kobe Central Civil Hospital, Kobe, Japan**

PANCREATODUODENECTOMY (PD) involves resection of the duodenum and the upper jejunum, an area in which inhibitory factors in gastric secretion are considered to be concentrated. The operation, moreover, causes impairment of pancreatic exocrine function, a reduction in buffering capacity because of biliary diversion, and maldigestion and malabsorption of lipids. As a result, the mucosa of the anastomosis sites is generally considered to become vulnerable to the attacks of both offensive and defensive factors. In PD, therefore, extensive gastrectomy including the pyloric sphincter[1–4] in combination with vagotomy is recommended for reduction in acid secretion.[5] In fact, there are many reports of marginal ulcers and hemorrhage of the gastrointestinal tract occurring after this operation.[6–9] In 1978, however, Traverso and Longmire performed PD without gastrectomy but by preserving the pyloric ring, with the whole stomach being supplied by the vagus nerve for postoperative functional preservation, with good results. They performed this stomach-preserving PD in a large series of patients, in some cases together with total pancreatectomy, but observed no postoperative hyperacidity or marginal ulcers.[11] However, some authors reported instances of hyperacidity followed by marginal ulcers in patients who had this operation,[12] and much remains to be elucidated about the pathogenic mechanism of this postoperative problem. We devised gastrobulbar preserving pancreatoduodenectomy (GPPD) with Billroth I type reconstruction on the basis of our hypothetical origin of this condition and studied exocrine and endocrine function of the stomach, a key factor in this problem, in patients who had GPPD and those who had conventional pancreatoduodenectomy (cPD).

Materials and Methods

Since the report of the first case in 1981,[13] we performed GPPD in more than 20 patients admitted to Kyoto University Hospital and its affiliate hospitals. Most patients with co-existing peptic ulcer or hyperacidity were excluded from indication of this surgery. Of those treated by GPPD, changes of exocrine and/or endocrine function of the stomach were examined in 13 (Table 1). The patients were eight men and five women, ranging in age from 29 to 74 years (mean: 56.1 years), including one who had total pancreatectomy. The final diagnoses of these patients were chronic pancreatitis in

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Submitted for publication: June 11, 1987.

TABLE 1. *Summary of Gastric Secretory Function Tests for 13 Patients Who Had Gastrobulbar Preserving Pancreatoduodenectomy (GPPD)*

Case	Age (Years)	Sex	Preoperative Diagnosis	Postoperative Diagnosis	Follow-up Period	Preoperative Acidity BAO Levels (mEq/h)	Preoperative Acidity MAO Levels (mEq/h)
1*	59	M	Sarcoma of the pancreas and duodenum	Myosarcoma of the pancreas and duodenum	11 mos	—	—
2†	59	F	Chronic pancreatitis	Cancer of the head of pancreas	1.5 mos	2.90	14.23
3	46	M	Leiomyoma of the duodenum	Unchanged	3 yrs 10 mos	2.74	27.63
4	56	M	Chronic pancreatitis	Unchanged	3 yrs 9 mos	0	0.36
5	67	F	Leiomyoma of the duodenum	Myosarcoma of the duodenum	10 mos	0	1.20
6	45	M	Chronic pancreatitis	Unchanged	3 yrs 8 mos	0.34	6.91
7	73	M	Chronic pancreatitis	Unchanged	3 yrs 9 mos	1.36	9.81
8	29	F	Anomalous arrangement of the pancreaticobiliary duct	Unchanged	3 yrs 8 mos	0.50	4.26
9	49	M	Chronic pancreatitis	Unchanged	3 yrs 5 mos	0.07	0.29
10	50	M	Chronic pancreatitis	Unchanged	1 yr 7 mos	0.09	0.25
11‡	64	M	Mucin-producing pancreatic cancer	Unchanged	1 yr 2 mos	0.003	0.03
12	60	F	Cancer of the ascending colon	Unchanged	3 mos	1.46	1.90
13	74	F	Cancer of the papilla of Vater	Unchanged	2 mos	0	0.98

* Preoperative acidity could not be determined because of retention of food in the stomach.

† *En bloc* resection was added 1.5 months after GPPD.

‡ Total pancreatectomy.

five, leiomyoma of the duodenum in one, anomalous arrangement of the pancreatobiliary duct in one, myosarcoma of the pancreas and duodenum in one, myosarcoma of the duodenum in one, cancer of the head of the pancreas (*en bloc* resection was added 1.5 months after GPPD) in one, cancer of the papilla of Vater in one, cancer of the ascending colon (formation of duodenal fistulas) in one, and mucin-producing pancreatic cancer in one. This operation was indicated, in principle, for benign diseases but was also performed in patients with sarcomas that infrequently show lymph node metastasis or localized early carcinomas unlikely to have metastasized, as well as in elderly persons and poor-risk cases. The patients were evaluated for 1.5 months to 3 years and 10 months (mean: 2 years and 1 month). Hyperacidic patients were, in principle, excluded from this surgery.

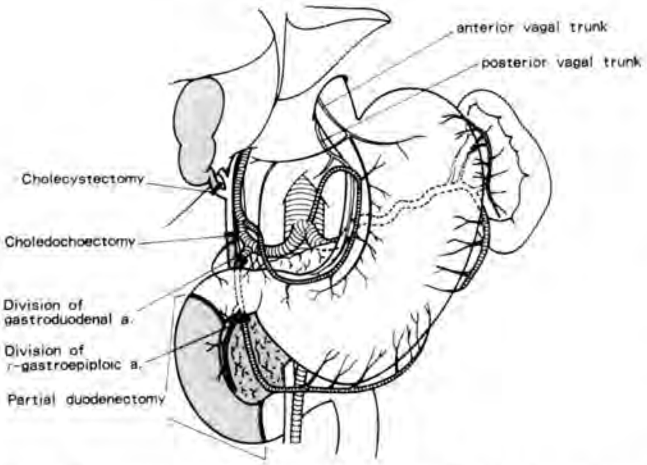

FIG. 1. Duodenectomy and vascular dissections. The duodenum is cut by access through the mouth at the upper margin of the second portion and through the anus at the third portion. The right gastroepiploic artery is ligated and cut just attached to the anterior surface of the pancreas, and the gastroduodenal artery is cut at the upper margin of the pancreas. Shaded area represents the area resected.

As shown in Figure 1, the duodenum was cut by entrance through the mouth at the upper margin of the second portion to leave the duodenal bulb intact, and by entrance through the anus, in principle, in the third portion oral from the area covered by the ligament of Treitz, preserving the distal duodenum and entire upper jejunum as much as possible. The head of the pancreas was usually cut above the portal system, and the gallbladder was resected. Caution was also exercised to preserve the vagus nerve, especially its pyloric and antral branches, left and right gastric arteries and veins, and other nerves and vessels supplying the entire stomach, including the gastroduodenal junction. The gastrointestinal tract was reconstructed retrocolically from the mouth to the anus by end-to-end duodenoduodenostomy, end-to-side pancreatojejunostomy, and end-to-side choledochojejunostomy by Billroth I procedure at intervals of about 10 and 5 cm (Fig. 2). No Braun's anastomosis was made. The pancreatic duct tube was led extracorporeally through the anterior wall of the stomach. Figure 3 is a roentgenogram of a patient's upper gastrointestinal tract 2 months after the operation. All patients survived the operation and were discharged.

The similar study was made in eight patients with cPD in whom 50–80% of distal stomach was resected. They consisted of five men and three women, ages 38–76 years (mean: 59.1 years): to be specific, six with cancer of the head of the pancreas, one with cancer of the papilla, one with pancreatic arteriovenous malformation, and one with chronic pancreatitis were studied 1 month to 3 years and 2 months (mean: 10.7 months) after the operation. None of these patients exhibited ulcer.

Nine male and four female healthy volunteers, ages 20–63 years (mean: 36.5 years), served as the normal controls.

Gastric Analysis

After patients had a 12-hour fast, gastric juice was collected through a gastric tube inserted nasally into the stomach so that changes in gastric secretion before and after pentagastrin injection (6 μg/kg, intramuscularly [I.M.]) could be studied. The gastric juice was collected at 10-minute intervals. The basal acid output (BAO) level was determined during the first 30 minutes, and after pentagastrin injection the maximum acid output (MAO) level was determined during the following hour. BAO and MAO levels represent 1-hour acid output. The examination was repeated from the time before to a maximum of 3 years and 10 months after the operation. Because there was some variation in the time of the examination among patients, changes in the acid level were serially studied in the same patients by division of the follow-up period into seven periods, namely, before; half a month; 1 month; 1 month to 1 year; 1–2 years; 2–3 years; and 3 years or more after the operation. The acidity of the gastric juice was titrated to an end point of pH 7.0 by use of a pH stat with 1/10 N NaOH and expressed as mEq.

Gastrin Determination

Blood was drawn from the antecubital vein early in the morning and 15, 30, 60, 90, and 120 minutes after the beginning of ingestion of a test meal consisting of ham, toast, one boiled egg, milk, and sugar (total weight, 365 g; protein, 21.6 g; fat, 19.7 g; carbohydrates, 58.4 g; total calories, 504). The serum was isolated and stored at −20 C until evaluation. The serum gastrin level was

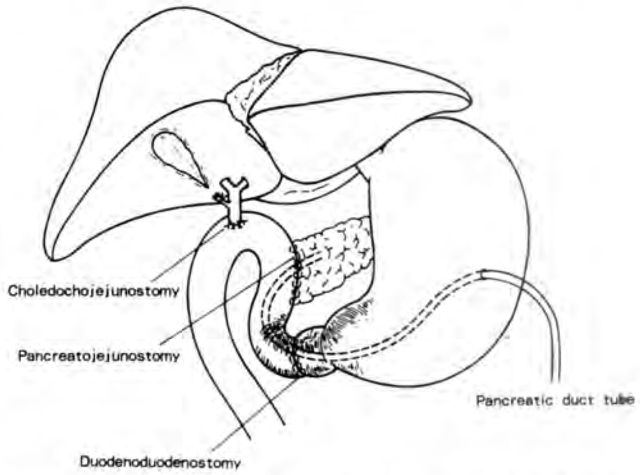

FIG. 2. Reconstruction of the digestive tract by our method. End-to-end duodenoduodenostomy, end-to-side pancreatojejunostomy, and choledochojejunostomy are performed from the mouth to the anus. The pancreatic duct tube is led extracorporeally through the anterior wall of the stomach. No Braun's anastomosis is made.

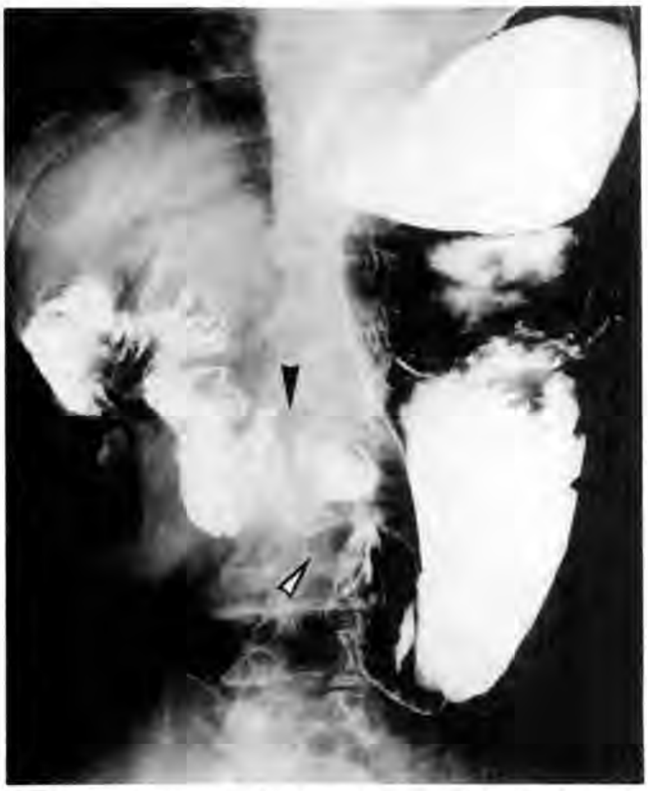

FIG. 3. A roentgenogram of the upper gastrointestinal tract 2 months after GPPD; ◁ = pyloric ring; ◀ = site of duodenoduodenostomy.

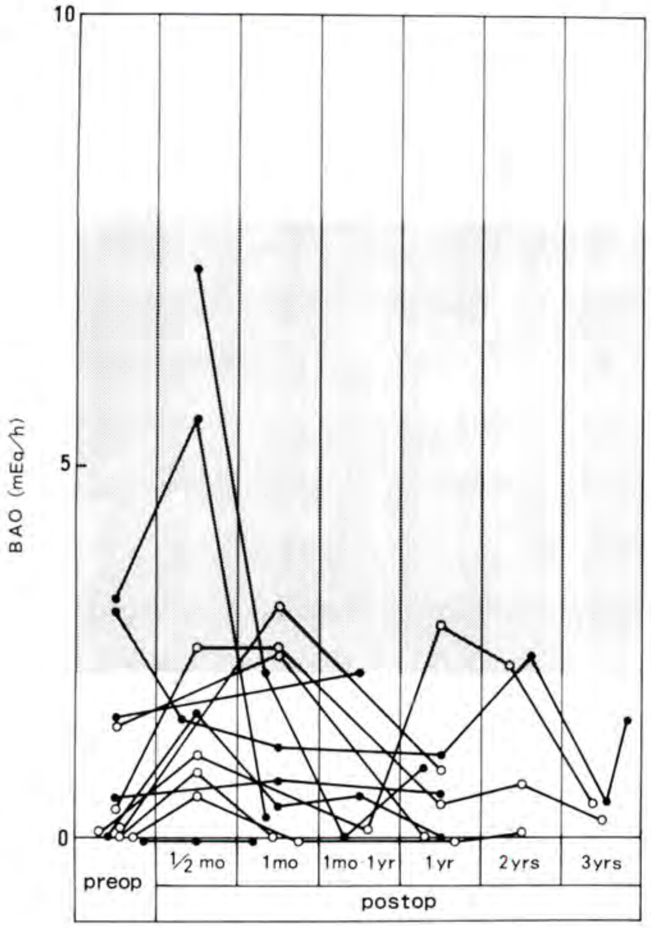

FIG. 4. Serial changes in BAO levels before and after GPPD. Shaded area represents the normal range; ○ = patients with chronic pancreatitis; ● = patients with nonchronic pancreatitis.

determined by use of a radioimmunoassay kit (CEA-IRA-SORIN Association, Gif-Sur-Yvette, France), and the basal gastrin level during fasting and the integrated gastrin response during 120 minutes after ingestion of the meal (IGR, the product of the mean gastrin level at each measurement after the meal and the interval until each measurement minus the product of the gastrin level before the meal and the total of all intervals) were calculated. Its changes were evaluated before as well as 1 month, 1–2 years, 2–3 years, and 3 years or more after the operation.

Postoperative Evaluation of the Gastrointestinal Tract

Symptoms and signs related to mucosal damage of the digestive organs including the sites of anastomosis were examined in all patients, and roentgenographs of the upper gastrointestinal tract were evaluated periodically. Endoscopic examination was also performed in four patients evaluated for more than 2 years and one patient evaluated for more than 1 year after the operation.

All values were expressed as mean plus or minus standard deviation (SD) and examined by unpaired Student's t-test. Correlations were calculated by parametric linear regression analysis, and $p < 0.05$ was considered to be statistically significant.

Results

Changes in Acid Output

BAO levels ranging from 2 to 8 mEq/h and MAO levels ranging from 5 to 21 mEq/h were regarded as normal (normoacidic). Values above or below these ranges were considered to indicate hyperacidity or hypoacidity, respectively.

Preoperative acid output. According to BAO levels, none of the patients was hyperacidic, two were normoacidic, seven were hypoacidic, and three were anacidic; according to MAO levels, one was hyperacidic, three were normoacidic, and eight were hypoacidic. The BAO or MAO level could not be determined in one patient with duodenal stenosis because of retention of a large volume of food in the stomach.

Postoperative changes in BAO levels (Fig. 4). BAO levels increased half a month after the operation but decreased after 1 month to a level comparable to the preoperative value in all patients except one, who showed duodenal stenosis before operation and in whom the BAO level tended to decrease immediately after the operation. The values were equal to or below the preoperative level 1 year after the operation and remained stable after more than 2–3 years. BAO levels were markedly increased in one patient 1 and 2 years after the operation, but the value remained in the normal range and decreased sharply after more than 3 years. BAO levels showed similar changes in those with and without chronic pancreatitis.

Postoperative changes in MAO levels (Fig. 5). MAO levels increased moderately half a month after the operation but decreased after 1 month, except in one patient with duodenal stenosis in whom the MAO level was high before the operation but rapidly decreased after the operation. The values were comparable to the preoperative levels 1 year after the operation, and no major changes were noted after more than 2–3 years. A marked increase was observed in one patient immediately after the operation, but the value decreased from a peak 1 year after the operation and remained within the normal range. Similar changes were observed in both those with and those without chronic pancreatitis.

Postoperative changes in BAO and MAO levels were similar.

Changes in Serum Gastrin Level

Changes in the basal gastrin level and IGR level during 120 minutes after the ingestion of test meal were studied in patients who could be examined repeatedly.

Basal gastrin levels ranging from 31.8 to 71.4 pg/mL and IGR levels ranging from 7.0 to 16.0 ng • min/mL were considered to be normal.

Changes in basal gastrin level (Fig. 6). Two patients with atrophic gastritis were markedly hypergastrinemic, two with chronic pancreatitis were mildly hypergastrinemic, and the other two showed normal gastrin levels before the operation.

The basal gastrin level decreased in most of the patients 1 month after the operation but increased 1 year after the operation and remained stable thereafter near the preoperative level. The basal gastrin level increased in two patients with chronic pancreatitis shortly after the operation but returned to normal after 2–3 years.

Changes in IGR levels (Fig. 7). One patient with atrophic gastritis was markedly hypergastrinemic, two with chronic pancreatitis were slightly hypergastrinemic, but the other two showed normal IGR levels before the operation.

IGR levels were reduced in all patients 1 month after operation but increased 1 year after operation in most patients and remained stable thereafter, near the normal level. In those with chronic pancreatitis, IGR levels were normal before the operation, increased abnormally after the operation, but returned near the normal level 3 years after the operation.

Relationship Between Gastric Acid Output and Gastrin Levels

The relationship between acid output and gastrin levels was examined in those available for evaluation by the use of all data from before and 1 month to 3 years after the operation. One patient with chronic pancreatitis (Patient 9), in whom both gastric acid output and gastrin level were abnormally enhanced after the operation, was excluded.

BAO and basal gastrin levels (Fig. 8). A significant negative correlation was observed for BAO and basal gastrin levels ($Y = -40.08X + 125.7$, $r = -0.479$, $p < 0.05$).

MAO and basal gastrin levels (Fig. 9). A significant negative correlation was observed for MAO and basal gastrin levels ($Y = -5.16X + 126.1$, $r = -0.476$, $p < 0.05$).

MAO and IGR levels (Fig. 10). A significant negative correlation was observed MAO and IGR levels ($Y = -0.66X + 17.26$, $r = -0.476$, $p < 0.05$).

Comparisons Between GPPD and cPD

Gastric acid output levels (Fig. 11). Gastric acid output levels were compared between 35 patients who had GPPD and nine patients who had cPD.

BAO levels. After operation, BAO levels were significantly higher ($p < 0.001$) in the group that had GPPD

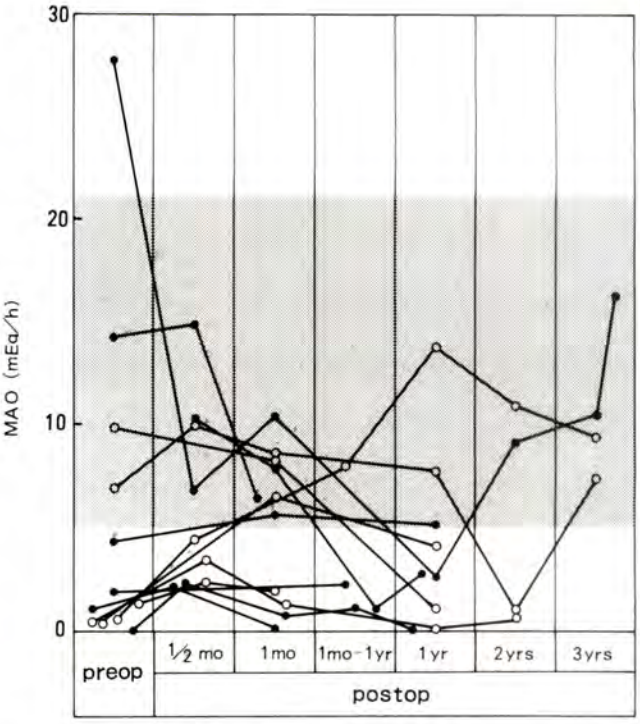

FIG. 5. Serial changes in MAO levels before and after GPPD. Shaded area represents the normal range; ○ = patients with chronic pancreatitis; ● = patients with nonchronic pancreatitis.

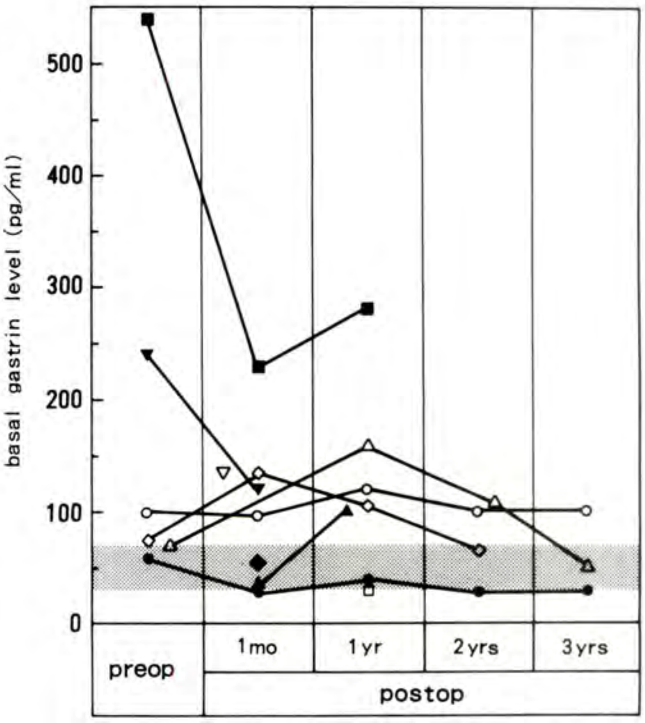

FIG. 6. Serial changes in basal gastrin levels before and after GPPD. Shaded area represents the normal range. Open symbols indicate patients with chronic pancreatitis. Closed symbols indicate patients with nonchronic pancreatitis.

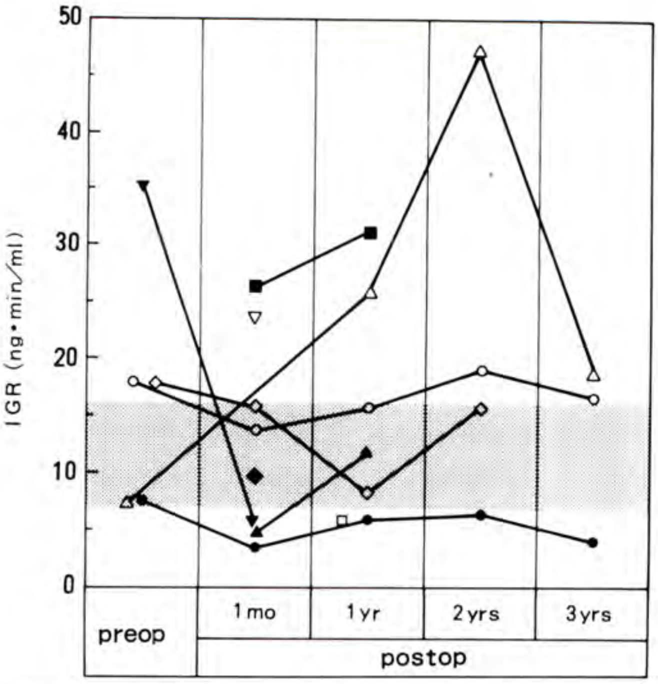

FIG. 7. Serial changes in IGR levels before and after GPPD. Shaded area represents the normal range. Open symbols indicate patients with chronic pancreatitis. Closed symbols indicate patients with nonchronic pancreatitis.

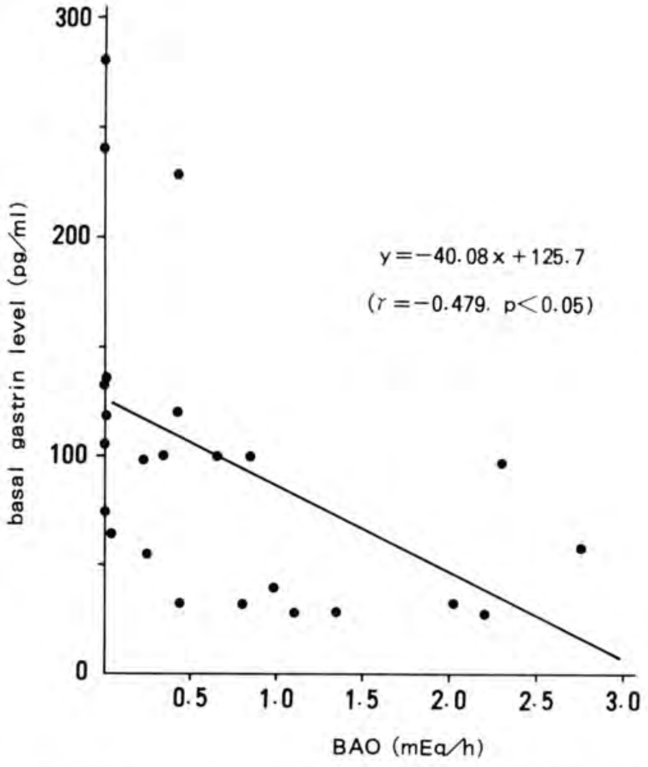

FIG. 8. Relationship between BAO and basal gastrin levels after GPPD.

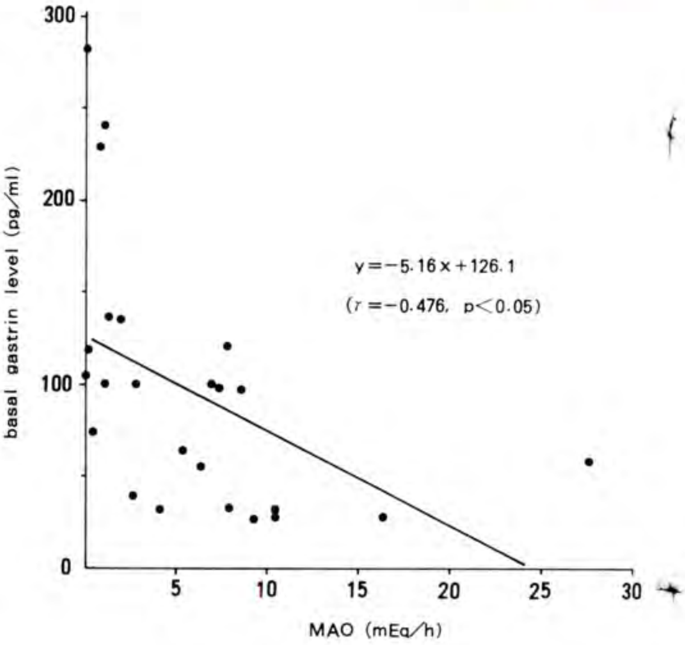

FIG. 9. Relationship between MAO and basal gastrin levels after GPPD.

(1.17 ± 1.55 mEq/h) than in the group that had cPD (0.04 ± 0.02 mEq/h) but were below the normal range.

MAO levels. After operation, MAO levels were significantly higher ($p < 0.001$) in the group that had GPPD (5.12 ± 4.29 mEq/h) than in the group that had cPD

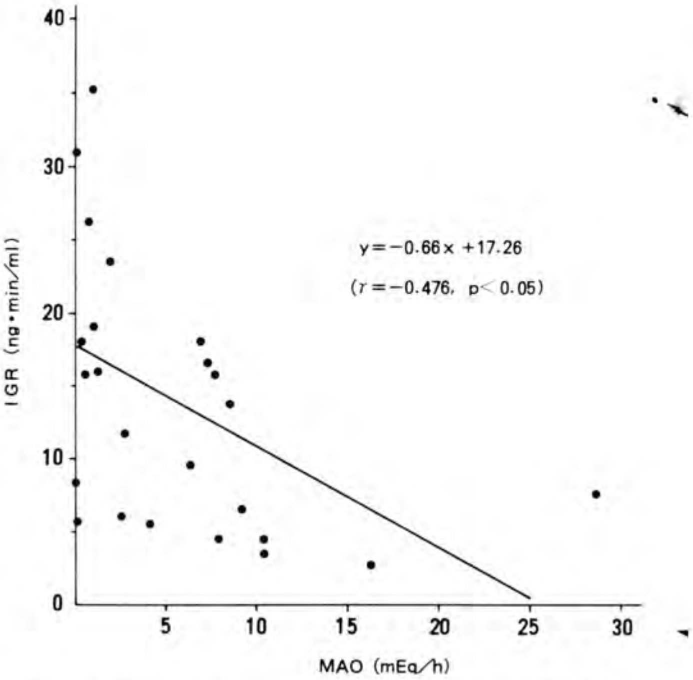

FIG. 10. Relationship between MAO and IGR levels after GPPD.

(0.54 ± 0.26 mEq/h), but the mean value was near the lower margin of the normal range.

Serum gastrin levels. Serum gastrin levels were compared among 20 patients who had GPPD, nine who had cPD, and 13 healthy controls.

Basal gastrin levels (Fig. 12). The basal gastrin levels were significantly higher after operation in the group that had GPPD (93.1 ± 66.6 pg/mL) than in both the group that had cPD (29.1 ± 6.5 pg/mL) and the control group (51.6 ± 19.8 pg/mL) ($p < 0.01$ and $p < 0.05$, respectively). The values in the group that had cPD were significantly lower ($p < 0.01$) than those of the control group.

IGR levels (Fig. 13). After operation, the IGR levels in the group that had GPPD (12.3 ± 7.9 ng•min/mL) were significantly higher ($p < 0.001$) than those in the group that had cPD (2.2 ± 1.5 ng•min/mL) but were not significantly different from those of the controls (11.5 ± 4.5 ng•min/mL). The values of the group that had cPD were significantly lower ($p < 0.001$) than those of the control group.

Postoperative Evaluation of the Gastrointestinal Tract

Most of the patients temporarily retained the gastric contents after the operation, but the condition was shortly resolved by repeated aspiration of the contents through an indwelling stomach tube. None of the patients had symptoms of mucosal damage of the digestive organs such as hematemesis and hematochezia throughout the observation period. Roentgenography was performed after operation in all patients, and endoscopic examination was done in those observed for a long time after the operation, but no signs of ulcer were observed in the stomach, duodenal bulb, or areas near the anastomoses. A patient (Patient 9) who showed marked enhancement of exocrine and endocrine stomach after the operation were examined more often and more closely than other patients, but no abnormalities were noted. One patient had GPPD with a diagnosis of chronic pancreatitis but was found by postoperative histologic examination to have pancreatic cancer and had *en bloc* resection of the upper gastrointestinal tract 1.5 months after the operation. Reddening was noted in the resected specimen of this patient in the jejunal mucosa anal from the anastomosis site, but there were no histologic findings suggestive of ulcer such as loss or rupture of the mucosa.

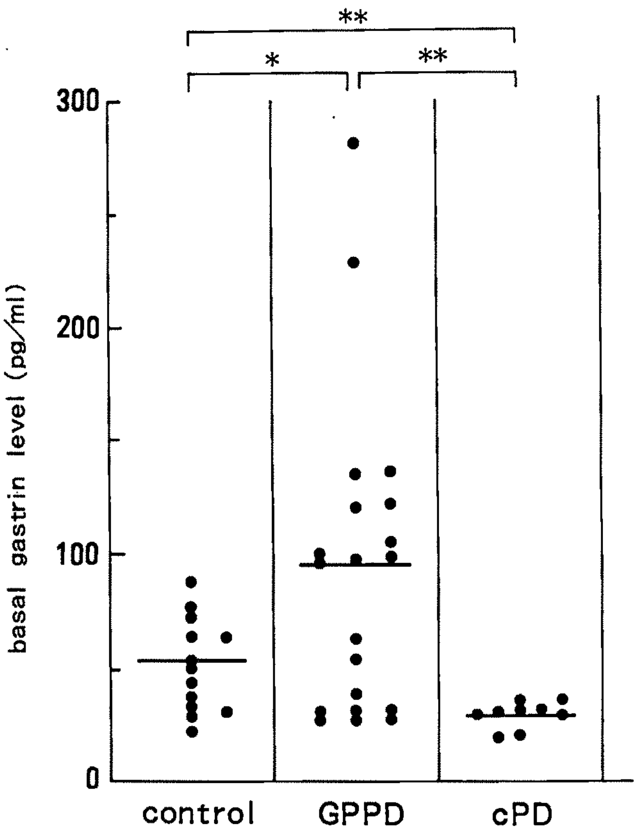

FIG. 12. Basal gastrin levels after GPPD and cPD. *p < 0.05; **p < 0.01.

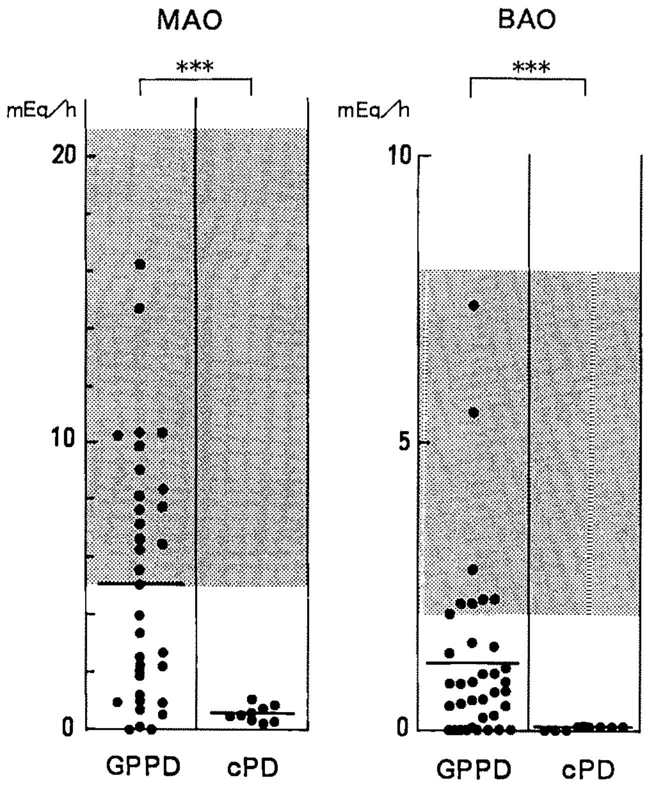

FIG. 11. BAO and MAO levels after GPPD and cPD. Shaded area represents the normal range; ***p < 0.001.

Discussion

Duodenectomy,[14,15] massive pancreatectomy (or pancreatic disorders),[16,17] and Mann-Williamson proce-

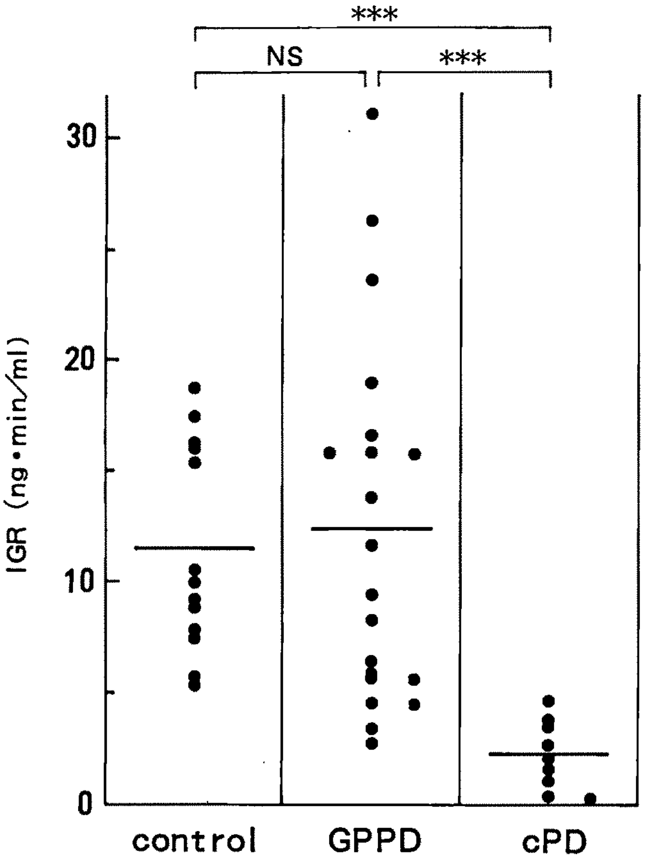

FIG. 13. IGR levels after GPPD and cPD. ***$p < 0.001$; NS = not significant.

dure,[18,19] in which bile and pancreatic juice are diverted through a duodenal segment to the distal intestine, frequently result in peptic ulcer in dogs. This condition is considered to result largely from increased acid secretion. Clinical pancreatoduedenectomy is considered to be associated with all these factors in peptic ulcer. Waddell et al.[1] studied changes in acid secretion after this operation and suggested that postoperative acid secretion increases, making the possibility of ulcer greater, as the extent of gastrectomy is smaller. In PD, therefore, some surgeons perform extensive gastrectomy, often in combination with vagotomy, to reduce acid secretion. However, there are still many patients who have marginal ulcers after this operation. The incidence of the condition is reported to be 6–36%,[4,6] and the mean interval between the operation and the onset of the disorder is reported to be 1.25 years by Grant et al.[4] and 3 years by Scott et al.[6] Contrary to this general view, Traverso and Longmire[10] attempted to preserve the entire stomach including the bulbar and pyloric regions in PD and found that the subsequent 18 patients treated by this procedure were free of ulcer and showed nearly normal acid secretion.[11] Among other studies, the incidence of the marginal ulcer after GPPD was reported to be low by Flautner et al. (0 of 37 patients, 0%),[20] Grace et al. (one of 37, 2.7%),[21] and Pearlman et al. (0 of 10, 0%),[22] but high by Braasch et al. (five of 87, 6%),[23] and particularly Gebhardt et al. (seven of 18, 38.9%), who reported the mean interval between the operation and the onset of ulcer to be 13 months. We studied changes in exocrine and endocrine stomach, a key factor in marginal ulcers after pancreatectomy and duodenectomy, with the occurrence of the condition in 13 patients from before to half a month to a maximum of 3 years and 10 months after GPPD (mean: 2.1 years).

As for gastric acid output, BAO and MAO levels showed similar changes after the operation. BAO and MAO levels temporarily increased half a month after the operation, decreased after 1 month, returned to the preoperative level after 1 year, and remained stable after more than 2–3 years. This temporary increase in acid output may be related to inadequate recovery of stomach muscle tone and peristalsis from the surgical insult[24] and poor gastric emptying secondary to disconnection of the proximal intestinal pacemaker,[25] in addition to partial loss of inhibitory factors in gastric acid secretion resulting from duodenectomy. As for gastrin level, both the basal gastrin level and IGR level after a test meal were reduced 1 month after the operation but returned nearly to the preoperative level after 1 year and remained near the normal level thereafter. Basso et al.[26] noted that, of those who had cPD, patients retaining antral mucosa after operation had marginal ulcers and bleeding stomitis develop and showed significant increases in bombesin-stimulated gastric acid output and gastrin level as compared with those without ulcer. Therefore, the long-standing postoperative control of gastrin level in our patients suggests that GPPD is advantageous for prevention of marginal ulcers and hemorrhage of the gastrointestinal tract.

The relationship between exocrine and endocrine stomach was studied next by use of all data from before to after GPPD, excluding one patient who showed marked increases in both acid output and gastrin levels. Negative correlations were observed between BAO and the basal gastrin levels, between MAO and the basal gastrin levels, and between MAO and IGR levels. The relationship between acid output and gastrin levels remains controversial, but Trudeau et al.[27] observed an inverse relationship between the basal gastrin level and both BAO and MAO levels in their subjects, who were patients with gastric ulcers, patients with duodenal ulcers, and healthy controls. Acid output levels were higher in patients with duodenal ulcer than in those with gastric ulcer or healthy controls, and the gastrin level in patients with gastric ulcer than in those with duodenal ulcer or healthy controls. They[28] also observed an increase in the gastrin level with the advance of age and ascribed this phenomenon to an age-associated reduction in acid secretion. Considering that none of our patients exhibited hyperacidity, gastric ulcer, or duodenal ulcer, acid output appears to be closely related to gastrin level except in those with hypoacidity resulting probably from old age. Gedde-Dahl[29] noted a negative correlation between pentagastrin-stimulated MAO and food-stimulated gastrin per cent increase response in normal humans. We, therefore, considered that a feedback mechanism is maintained between parietal cells and G cells during fast as well as after meals from before to after GPPD.

However, in one patient (Patient 9), who showed an abnormal increase in acid and gastrin levels after operation, negative correlation was not observed between those from before the operation. It is likely because of failure to maintain the feedback mechanism.

An increase in gastric acid secretion was observed in dogs in association with pancreatic exocrine dysfunction, and the condition was ascribed primarily to hypergastrinemia.[16,17] Gastric acid secretion has often been reported to decrease in patients with chronic pancreatitis.[30-32] Gulbo et al.[33] compared the basal gastrin levels and gastrin response levels after a meal between patients with chronic pancreatitis and normal controls but noted no significant difference between the two groups. As in other studies, almost all patients of this study were normoacidic or hypoacidic before the operation. Grant et al.[4] suggested that the incidence of post-PD ulcer is higher in patients with than without chronic pancreatitis, but we observed similar changes in acid secretion in both those with and those without chronic pancreatitis. As for gastrin levels, both the basal gastrin and IGR levels showed slight increases before the operation in the small number of patients examined, but the basal gastrin level increased but IGR showed no significant difference after the operation as compared with the controls. These differences in changes in acid and gastrin levels may result from to atrophic gastritis not involving the antrum, as suggested by Gulbo et al.,[33] or to hypoacidity secondary to other causes.

Next, postoperative acid output and gastrin response levels were compared between GPPD and cPD. Acid output levels were clearly lower in our patients than those of Pearlman et al.[22] In those who had underwent cPD, they were similar to those in the series of Sato et al.,[34] despite the difference in the method of stimulation, but were lower than in the series of Waddel et al.[1] In patients who had GPPD, both BAO and MAO levels were higher than in those who had cPD, but the mean value was near the lower margin of the normoacidic range. These findings indicate that acid output is maintained near the normal level after GPPD, whereas it is markedly reduced after cPD because of extensive gastrectomy. As for gastrin level, basal gastrin levels were significantly higher in those who had GPPD than in the controls, but IGR levels were not significantly different between the two groups. The higher basal gastrin levels in patients with GPPD than in the controls result from the presence of a few patients with hypergastrinemia associated with anacidity.[35,36] Both the basal gastrin and IGR levels were lower in those who had cPD than in those who had GPPD or the normal controls, clearly because of the antrectomy.

We periodically examined all patients by radiography and endoscopy of the upper gastrointestinal tract but did not encounter ulcer of the anastomosis sites or mucosal damage. These findings suggest that there are no major problems concerning offensive factors after GPPD.

Some investigators[37,38] considered that the primary pyloric function is to prevent reflux. Fisher et al.[37] postulated a sequence of events triggered by reflux of bile-containing duodenal contents into the stomach because of pyloric incompetence and resulting in gastric ulcer formation. Nahrwald[39] also demonstrated that in dogs, antral retention of bile and bile acid could release gastrin. Braasch,[40] moreover, considered that the loss of a pylorus could allow alkaline reflux, antral stimulation, subsequent parietal cell stimulation, and resulting increased gastric secretion and that pyloric preservation can prevent jejunal ulcer formation by preventing this possible chain of events.

The duodenal bulb is considered to play an even greater role than the pylorus in prevention of ulceration after this operation. The duodenal bulb possesses an acid-sensitive mechanism and plays a primary role in duodenal inhibition by releasing gastric inhibitory hormones such as somatostatin,[41] bulbogastrone,[42] and secretin,[43] as well as regulating gastric emptying.[44] A pacemaker is present within 1 cm from the pylorus to control the transport of the gastric contents.[45] The Brunner's glands distributed primarily in the bulb neutralize the gastric acid by secreting mucus and bicarbonates to protect the duodenal mucosa.[46]

Because we understand that ulceration is prevented by cooperative actions of the pylorus and the duodenal bulb, we called our procedure gastrobulbar preserving pancreatoduodenectomy.

However, despite these precautions, Braasch et al.[23] observed ulcer formation in five of their 87 patients, including 13 who had total pancreatectomy. Gebhardt et al.[12] noted the condition in seven of 18 patients, more frequently in those showing enhanced gastric acid secretion after the operation. They concluded that the duodenal bulb alone cannot adequately inhibit acid secretion. By their method of reconstruction, the oral extremity of the remaining intestine is left empty in a blind loop, and, apart from this site, a further anal portion of the intestine is anastomosed end-to-end with the duodenum. By this procedure, the portion of the intestine lacking protection for mucosa and containing less gastric inhibitory factors is directly exposed to the gastric juice. In addition, because the blind intestine is anastomosed end-to-side further anally from the site of the influx of gastric juice, the duodenal anastomosis site is not adequately neutralized by bile or pancreatic juice.

Kiriluk et al.[47] showed that in dogs the buffering capacity of the bowel contents is progressively reduced as the distance from the pylorus is increased. In the humans, unlike dogs, Brunner's glands are not only densely distributed in the proximal duodenum, but are considered to also be present in the distal duodenum,[46] giving this portion a buffering ability.[48] Moreover, Isenberg et al.[49] observed that bicarbonate secretion from the bulb is increased by stimulating the distal duodenum, not to mention the bulb, with acid.

We devised our GPPD for preservation of defensive factors, cutting the duodenum with access through the mouth in the second portion, to leave the bulb intact, and from the anus, in principle, in the third portion, to minimize the area of duodenectomy, and reconstructing the duodenum by end-to-end anastomosis. Just anal to this duodenodeodenostomy, end-to-side pancreatojejunostomy and then end-to-side choledochojejunostomy were made without any Braun's anostomosis. Thus, we tried, on the one hand, to reduce acid secretion and preserve defensive mechanisms, and, on the other, to neutralize gastric acids by maintaining adequate bile and pancreatic juice output levels *via* secretion of gut hormones distributed in this region.[50] Also, pancreatojejunostomy performed just proximally will permit rapid neutralization of acid by pancreatic juice and choledochojujunostomy distally will prevent reflux of bile into the stomach.

These surgical manipulations together with exclusion of patients susceptible for peptic ulcer, such as those showing ulcer or hyperacidity before the operation as well as those with a history of ulcer, are considered to have contributed to prevention of marginal ulcers in our patients.

Conclusion

In our GPPD, the extent of duodenectomy is minimized, the neurovascular supply to the pylorus and duodenal bulb is preserved, and the intestine is reconstructed by end-to-end duodenoduodenostomy that is Billroth I type. This procedure ensures rhythmic discharge of gastric acid first into the duodenal bulb, which is resistant to mucosal damage; its transport through the site of duodenoduodenostomy to the upper jejunum while stimulating release of gastric inhibitory factors; and adequate stimulation of bile and pancreatic secretion. As a result, acid is efficiently buffered and pancreatic enzymes thoroughly activated,[51] to allow smooth digestion and absorption of lipids, and the gastric inhibitory factor (enterogastrone)[52] is released to prevent abnormal increases in acid secretion.

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Percutaneous Ultrasonography-guided Cutting Biopsy from Liver Metastases of Endocrine Gastrointestinal Tumors

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Ultrasonography-guided cutting needle biopsy of the liver was performed in 186 instances on 95 different patients with carcinoid and endocrine pancreatic tumors. In 171 cases, biopsy specimens were taken from liver metastases found on ultrasonography, and in 93% of these the obtained material was adequate for a correct diagnosis. In the 7% for which an incorrect diagnosis was made, all but one biopsy specimen contained normal liver tissue, indicating that the needle-guiding technique, and not the sampling technique, is the most critical part of the biopsy procedure. Tumor specimens were examined with silver stains and immunocytochemistry after application of monoclonal serotonin antibodies. The argyrophil silver stain of Grimelius could be applied on all specimens and had positive results in all but one case, demonstrating the neurohormonal endocrine origin of the metastases. The argentaffin reaction and/or serotonin immunoreactivity could be applied in 152 cases and had positive results in 115 of 122 (94%) of the mid-gut carcinoid tumors and negative results in 27 of 28 (96.4%) of the non–mid-gut carcinoid tumors and endocrine pancreatic tumors. Major complications occurred in 1.5%; none was lethal or required surgery. The results show that the technique used for tumor biopsy is very accurate and provides material sufficient for multiple histopathologic and immunocytochemical analyses without exposing the patients to high complication risks. It is further concluded that the staining techniques and immunocytochemical analyses applied on the biopsy specimens are valid for the prediction of the location of the primary endocrine tumor.

PERCUTANEOUS FINE-NEEDLE BIOPSY of liver metastases has been routinely used to confirm the diagnosis, because cytologic examination usually reveals whether or not a lesion is malignant.[1,2] Cutting biopsy, with needles of larger dimensions, has been used mainly for diagnosis of diffuse liver disease, where fine-needle cytologic procedures are insufficient.[3-5] Fine-needle biopsy is used, instead of cutting biopsy, in focal liver disease because of the lower risk of complications, for example, bleeding.[6]

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In patients with endocrine tumors derived from the neuroendocrine cell system, liver metastases are often present at the time of hospital admittance. Cutting biopsy specimens can be examined both with histopathologic and histochemical techniques and immunocytochemical analyses, making it possible, with a high degree of accuracy, to establish the histopathologic diagnosis and the topographic location of the primary tumor.[7]

The aim of this investigation was to examine whether ultrasonography-guided cutting biopsies are adequate to sample material for histologic and immunocytochemical analyses. The staining techniques for endocrine cells and hormones for predicting the location of the primary tumor were also investigated, as was the complication rate of the biopsy technique.

Materials and Methods

One hundred eighty-six liver biopsy specimens, taken from 95 different patients with carcinoid tumors or endocrine pancreatic tumors (EPTs), were examined. There were 40 men and 55 women; the mean age was 60.8 years and the median age 63 years (range: 18–78 years). All patients were examined with ultrasonography before liver biopsy was performed with ultrasonographic guidance.[7-9] All biopsies were taken with either a Tru-Cut (Travenol, France) or Biopty (Radioplast A.B., Sweden) needle with an external outside diameter of 2 mm (173 cases) or 1.2 mm (11 cases). In two cases biopsies were performed with both 2.0-mm and 1.2-mm needles. The needle was placed in an automatic biopsy de-

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vice (Fig. 1), making it possible to perform the biopsy with one hand while holding the ultrasound transducer with the other.[8] If the liver mass was large or showed ultrasonographic features of tumor necrosis, attempts were made to obtain the biopsy specimen from the periphery of the lesion. All patients were hospitalized during the biopsy procedure, and normal bleeding and coagulation parameters were required (platelet count, Normotest [NYCOMED A. S., Oslo, Norway] Activated Prothrombin Time [NYCOMED A. S.]) for a biopsy procedure. All patients were kept in bed for 4 hours after biopsy and stayed overnight in the hospital.

Light Microscopy

The biopsy specimens were divided and fixed in 10% buffered formalin or in Bouin's fluid, dehydrated, and embedded in paraffin. Sections, approximately 4-μm thick, were cut and stained with hematoxylin and eosin, van Gieson stain, the argentaffin reaction of Masson, and the argyrophil reactions of Grimelius and Sevier-Munger.

Immunocytochemical Analysis

Immunocytochemical analysis with monoclonal serotonin antibodies (Mas 055 clone YC5/45, HLK SeraLab Limited, Crawley Down, Sussex, England) was used for visualization of serotonin-containing endocrine tumor cells.[7]

Analysis of Complications

Notes of any complications were registered in the patients' medical records.

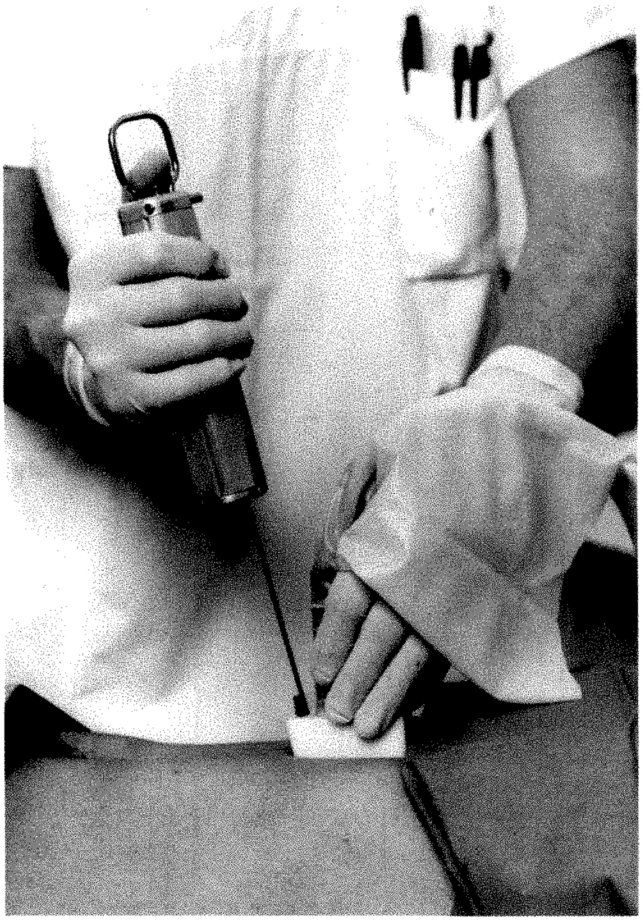


FIG. 1. The biopsy device is loaded with a specially designed cutting needle and introduced into the tissues through the needle guide unit attached to the ultrasound scan head. The device makes it possible to perform the sampling procedure swiftly with just one hand.

Results

Biopsy results were classified as "correct diagnosis" and "incorrect diagnosis" (Fig. 2), where biopsy results were considered correct if the biopsy diagnosis agreed with the final diagnosis. If the biopsy examination, for example, showed normal liver tissue and follow-up evaluation showed metastatic liver disease or the biopsy examination showed malignant tumor tissue but the endocrine nature of the tumor was not indicated, the biopsy results were classified as incorrect. In 10 cases no abnormality was detected with ultrasonographic examination, but biopsy was performed and examination showed (Fig. 2) normal liver tissue in nine cases and carcinoid tumor in one. In three of the cases with normal liver tissue in the biopsy specimens, two with EPTs and one with a carcinoid tumor, multiple metastases smaller than 1 cm were noted at angiographic examination and operation. The remaining six showed no signs of liver metastases with other examinations or at operation. In five ultrasonographic examinations, diffuse changes of the liver parenchyma were seen. In four of these, biopsy results and final diagnosis agreed (three steatosis and one diffuse carcinoid tumor infiltration) and in one case the biopsy specimen and ultrasonographic examination showed fatty infiltration, whereas angiographic examination revealed several small metastases, 4–6 mm in diameter. In the 171 cases where biopsy specimens were taken from focal masses in the liver, biopsy results and final diagnosis agreed in 159 cases (93%). In 12 cases the biopsy results were classified as incorrect. One of these biopsy specimens showed "low differentiated malignant tumor," whereas the final diagnosis was metastasis from an EPT. The remaining 11 biopsy specimens all contained normal liver tissue, and the tumor had consequently been missed. Eight of these tumors were smaller than 1.5 cm and none larger than 3 cm. Most also had an unfavorable location in the dome of the right lobe of the liver, close to the diaphragm. In the whole material of 171 liver metastases

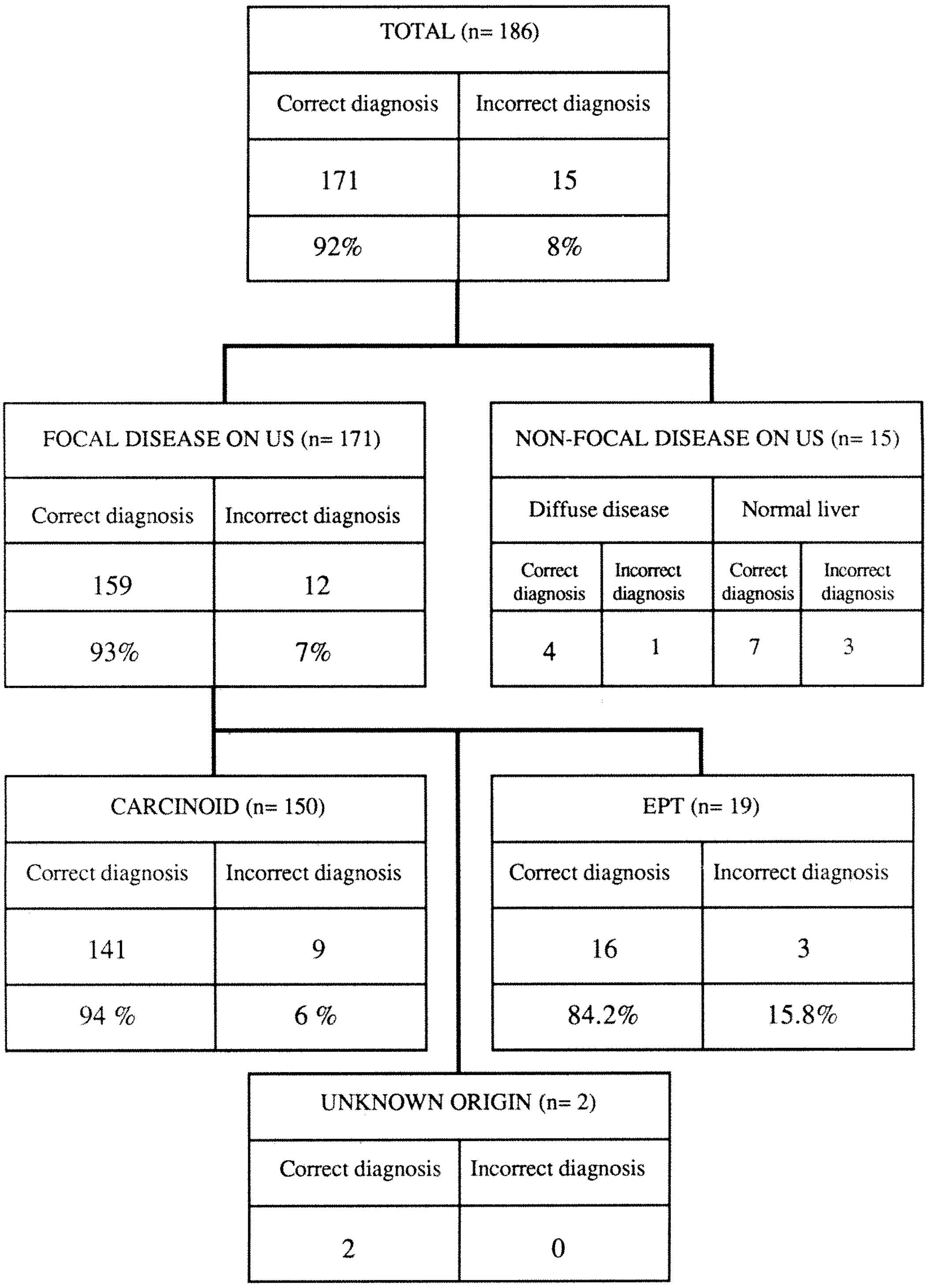


FIG. 2. The results of microscopic examinations of biopsy specimens; US = ultrasonography; EPT = endocrine pancreatic tumor.

for which biopsies were done, the tumor size varied between 1 and 20 cm (mean: 4.1 cm).

To test the accuracy of the analyses for identifying the topographic location of the primary tumor, the 162 specimens containing tumor tissue were compared with the known location of the primary tumor (Table 1). A tumor was classified as a "mid-gut carcinoid tumor" if the primary site was located between the duodenum and the left flexure of the colon. Carcinoid tumors from the gastrointestinal tract above the duodenum (foregut) and below the left colonic flexure (hindgut) and those with the primary site outside the gastrointestinal tract (lung) were classified as "non-mid-gut carcinoid tumors." In 10 biopsy specimens the amount of material was not

TABLE 1. *The Results from Silver Stains and Immunoreactivity to Monoclonal Serotonin Antibodies in Biopsy Specimens Correlated to the Location of the Primary Tumor*

Tumor	G+ M− SI−	G+ M/SI+	G− M− SI−	G+ M = 0 SI = 0	Number of Biopsies
Mid-gut	7	115	0	7	129
Non–mid-gut	11	1	0	1	13
EPT	15	0	1	2	18
Unknown origin	2	0	0	0	2
Total					162

G = Grimelius argyrophil stain; M = argentaffin reaction of Masson; SI = serotonin immunoreactivity; + = positive reaction; − = negative reaction; 0 = not tested; M/SI+ = positive argentaffin reaction and serotonin immunoreactivity or one of the reactions positive and the other not tested.

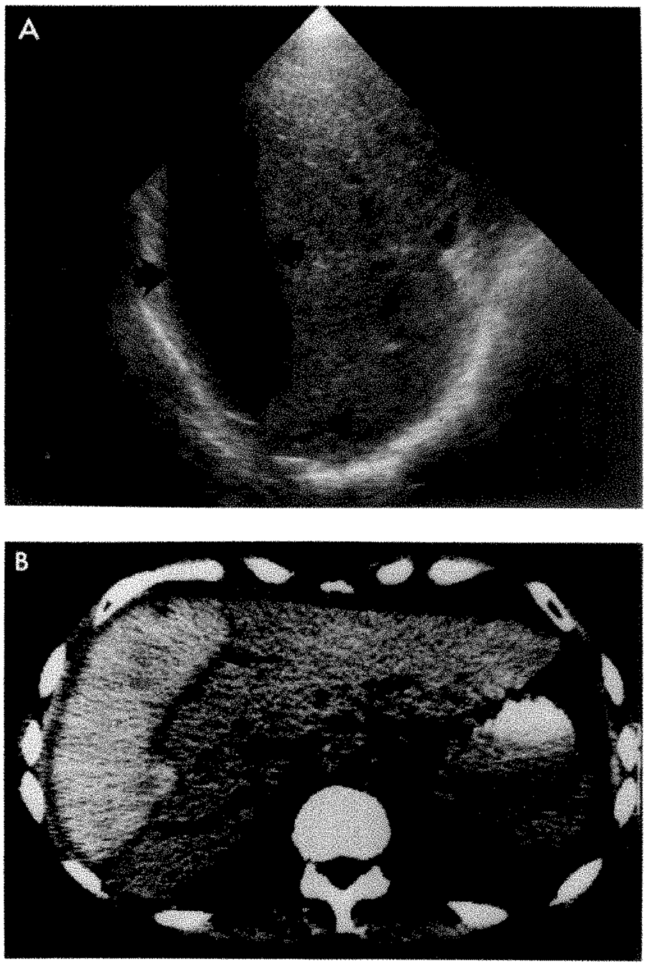
enough to allow all analyses to be performed, and neither the argentaffin reaction nor immunocytochemistry could be analyzed (seven mid-gut tumors, one non–mid-gut tumor, and two EPTs). In the remaining 152 specimens (122 mid-gut carcinoid tumors, 12 non–mid-gut carcinoid tumors, 16 EPTs, and two tumors of unknown origin), the material was sufficient for adequate analysis, but eight specimens (all mid-gut tumors) only permitted examination with one of the two methods indicating serotonin content. In the group of mid-gut tumors, seven specimens showed negative argentaffin reaction and/or negative serotonin immunoreactivity (5.7%), whereas one of the specimens from the non–mid-gut tumor group showed a weakly positive reaction. All but one of the patients with mid-gut tumors and a negative argentaffin reaction or serotonin immunoreactivity later had rebiopsies, and all these biopsy specimens showed a positive argentaffin reaction. In the group with EPTs, no specimen showed positive argentaffin reaction or positive serotonin immunoreactivity. In two cases the location of the primary lesion could not be established, both specimens showing negative argentaffin reaction. With one exception, all specimens containing tumor tissue showed a positive reaction for Grimelius argyrophil silver nitrate stain. This case with normal results was incorrectly classified as "low differentiated tumor."

In the 11 specimens obtained with the 1.2-mm needle, normal liver tissue was found in two and tumor tissue in nine. In all the nine specimens containing tumor tissue, the amount of material was sufficient to allow both a complete light microscopic examination and immunocytochemical analysis to be performed.

Three major complications occurred—all intrahepatic hematomas occurring after biopsy with the 2.0-mm needle (Fig. 3). In all three patients multiple biopsies (more than three) were performed. None of the patients required surgery. No other major complications were noted, but several patients had various degrees of pain lasting for minutes up to 10 days, most episodes lasting a few hours.

Discussion

The results show that percutaneous biopsy under ultrasonographic guidance is an extremely safe and reliable method for obtaining material from liver tumors for histopathologic examinations because adequate material was obtained in 93% of the tissue specimens, al-



FIGS. 3A and B. Ultrasonographic (*A*) and computed tomographic (*B*) scans of the liver in a patient with a postbiopsy hematoma in the right lobe (arrows).

lowing the pathologist to make the correct diagnosis. Among the 7% of the specimens from focal lesions not giving the correct diagnosis, only one case showed tumor material and the rest showed normal liver tissue. It is therefore probable that the guidance of the biopsy needle into the lesion is the most critical procedure where most failures occur. This is also supported by the fact that all but one of the patients with an incorrect diagnosis had small tumors (<3 cm) usually unfavorably located high up in the dome of the liver. The automatic biopsy device gave enough material to allow a tumor diagnosis in all cases where tumor tissue was present in the specimen, but in a small number of cases (10 of 162 specimens with tumor tissue) the amount of material was not sufficient for performance of all analyses. In the 14 cases where no focal lesion, or obvious diffuse tumor infiltration, was present, tumor tissue was obtained in only one case, whereas angiographic examination revealed metastases in an additional four cases. It therefore seems meaningless to take biopsy specimens blindly from a liver that appears normal on ultrasonographic examination.

There were no differences between the 1.2- and 2-mm biopsy needles in obtaining enough material for the histopathologic and immunocytochemical analyses. The use of the 2.0-mm needle is therefore abandoned, although the number of major complications was low (1.5%), because the use of a smaller needle may further reduce the risk for complications.

The silver stains employed on the biopsy specimens have an affinity for hormone secretory granules in normal and neoplastic endocrine cells and make it possible to visualize these structures on light microscopic examination.[10] The Grimelius argyrophil stain is specific for endocrine cells and tumors of the neurohormonal type but is nondiscriminatory, because a positive reaction is obtained in most carcinoid tumors and EPTs, irrespective of their hormone content.[10] The argentaffin reaction of Masson, on the other hand, is specific for carcinoid tumors with content of serotonin, which is characteristic of mid-gut carcinoid tumors (classic carcinoids).[11] These observations make it possible to differentiate mid-gut carcinoid tumors from non–mid-gut carcinoid tumors and EPTs. Our investigation confirms that the silver staining characteristics of the primary tumor are also found in the secondary lesions, making it possible to indicate the location of the primary tumor after examining biopsy specimens from liver metastases. The accordance between the topographic location of the carcinoid tumor and the presence or absence of proven serotonin content is not complete, however. In seven cases, negative argentaffin reactions and/or negative serotonin immunoreactivity were present in specimens from mid-gut carcinoid tumors. This may be because the serotonin content of classic mid-gut carcinoid tumors is unevenly distributed within the tumor and areas without serotonin may be found in between the serotonin-containing ones, which is supported by our observation that, in all but one case, subsequent biopsy specimens showed a positive argentaffin reaction. To reduce the number of biopsy specimens with serotonin-negative material, it may be justified to take two, or more, biopsy specimens from different areas of a metastasis. The use of the two different methods to show the serotonin content is recommended because the methods are valid on different tissue fixation specimens—the argentaffin reaction of Masson on formalin-fixed tissue and serotonin immunoreactivity on Bouin-fixed material. This means that if the obtained biopsy material fixed in one fluid is sparse, the tissue fixed with the other method possibly can be analyzed adequately, which occurred in eight cases with this material. The Grimelius argyrophil silver nitrate stain had a positive reaction on all tumor specimens but one, indicating that the method is extremely reliable in showing the endocrine origin of the metastatic lesions.

Although the risks with the biopsy method used are low, they could be minimized even more by use of a smaller needle and not performing more than three biopsies at the same investigation.

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Portal Vein Injuries

Noninvasive Follow-up of Venorrhaphy

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The authors report their experience with 14 patients with portal vein injuries (1976–1986) treated at a level I trauma center. Seven patients (50%) survived and included six of 10 patients (60%) who had venorrhaphy and one in whom the portal vein was ligated. Associated injuries were present in all the patients (mean Abdominal Trauma Index: 39.5) and accounted for the high mortality rate. Follow-up data after repair or ligation of the portal vein seldom are reported in the literature. The authors studied all three patients who survived portal venorrhaphy since 1982 by real-time ultrasonography. Patency of the repair could be established in two patients. In the third patient postvenorrhaphy thrombosis was diagnosed by ultrasonographic examination. Sequential ultrasonographic examinations demonstrated resolution of the thrombus on anticoagulant therapy. Ultrasonography provides a noninvasive and easily reproducible method of studying the portal vein after repair.

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TRAUMA to the portal vein is rare. In the last three decades fewer than 200 such injuries have been described in the literature.[1-13] The largest series from a busy trauma center[10] spanned a period of 23 years and included only 46 patients. These injuries often are lethal; the reported mortality rate resulting from uncontrolled hemorrhage varies from 50 to 70%. The frequent occurrence of concomitant injuries to other major organs and vascular structures, along with the technical difficulty of isolating and controlling the lacerated portal vein, contributes to this high mortality rate. Lateral venorrhaphy is the preferred method of management of the injured portal vein. More recently, however, it has been suggested that ligation of the vein is a viable alternative in patients with unstable conditions.[7,8,10] Although there has been a significant survival rate after portal vein ligation, postvenorrhaphy thrombosis of the portal vein as a fatal complication has been reported by Fish[2] and Chisolm and Lenio.[3] Portal vein thrombosis after repair may complicate postoperative fluid and electrolyte management as a result of splanchnic bed sequestration.[12,14] Unfortunately, the real incidence of portal vein thrombosis after repair has not been investigated, probably because of the relative difficulty in investigating the portal system in critically injured and hemodynamically unstable patients.

In this report we present our experience with portal vein injuries, with particular emphasis on a noninvasive modality for the study of the repaired portal vein. To our knowledge, this is the first report of such a follow-up in a series of patients with portal vein trauma.

Clinical Materials and Methods

Between 1976 and 1986, 14 patients with portal vein injuries were treated at the Lincoln Medical and Mental Health Center, a level I trauma center. There were 12 men and two women, with an age range of 22–36 years. Seven patients were stabbed, and seven received gunshot wounds. All the patients had hypotension (systolic blood pressure less than 90 mmHg) on admission. Five patients had no palpable blood pressure. Two patients had emergency room thoractomies for resuscitation, and in two others thoracotomies were performed in the operating room for aortic compression in an attempt to reduce intra-abdominal hemorrhage. None of these patients who were *in extremis* survived.

Associated injuries were noted in all of the 14 patients (Table 1), the liver being the most common organ injured. An associated bile duct injury was found in three

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TABLE 1. *Associated Injuries*

Visceral Injuries		Vascular Injuries		
Location	No. of Patients	Location	No. of Patients	(No. of Survivors)
Liver	10	Hepatic artery	2	(1)
Pancreas	3	Superior mesenteric	3	(0)
Duodenum	3	Inferior vena cava	3	(2)
Spleen	1	Aorta	3	(1)
Biliary tract	4	Renal vessels	3	(2)

patients. One patient, with a severe crush injury of the duodenum and the head of the pancreas, required a pancreatoduodenectomy as well as portal and vena caval repair. Major vascular injuries were common (eight of 14 patients, 57%) and involved the hepatic artery (two patients) and the aorta, vena cava, and their tributaries (12 injuries in six patients). The mean abdominal trauma index of 39.6 testifies to the severity of trauma sustained. The patients received a mean of 10 units of packed erythrocytes (range: 6–26 units).

The portal vein injury was managed by ligation in one patient and venorrhaphy in 10 patients. Three patients died from exsanguination before repair could be attempted. Seven of the 14 patients (50%) survived, including the patient treated by portal vein ligation. Six of the 10 patients who had venorrhaphy survived. None of the four patients who required resuscitative thoracotomy survived. Five of the seven deaths occurred during operation, and two patients died in the intensive care unit. All the deaths resulted from a combination of uncontrolled bleeding and coagulopathy. The survivors had a mean Abdominal Trauma Index of 28.1, whereas the Index was 51 for those who did not survive. Four of the eight patients with concomitant major vascular injuries survived.

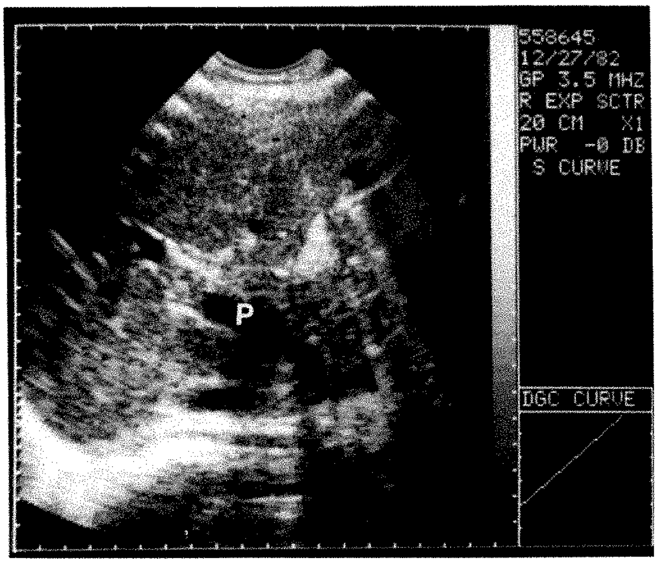

FIG. 1. Right oblique parasaggittal view demonstrating thrombus (arrow) within the portal vein (P) with near-total occlusion of the lumen.

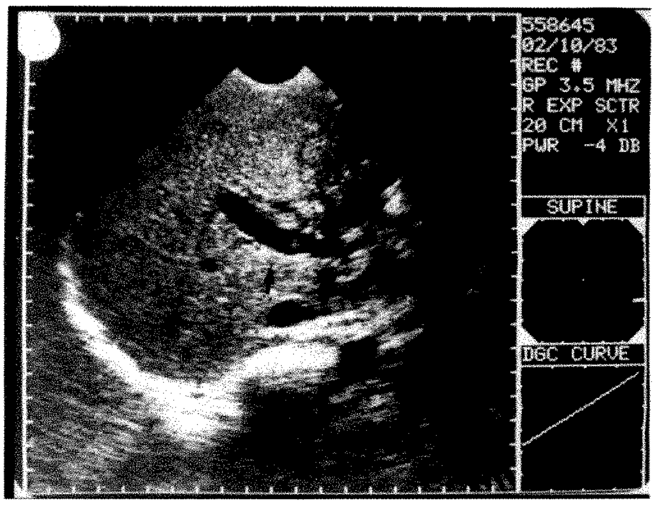

FIG. 2. Left oblique parasaggittal view after 5 weeks of anticoagulation showing resolution of the thrombus.

Follow-up of the Repaired Portal Vein

Since 1982, three of seven patients with portal vein injuries lived. In these patients, the portal vein was studied after operation by real-time ultrasonography. The first patient, who had sustained injuries to the portal vein and common hepatic duct that were treated by venorrhaphy and biliary ductal repair, had ultrasonographic examination of the abdomen on the 16th day after operation for a suspected intra-abdominal abscess. None was found. Instead, in the real-time study, blood could be seen swirling past an echogenic density that almost completely occluded the lumen of the portal vein (Fig. 1). Portal vein thrombosis was diagnosed. The patient was treated with continuous intravenous heparin therapy. In subsequent weeks, the patient improved clinically, and sequential ultrasonographic examination demonstrated resolution of the thrombus with complete restoration of the venous lumen of the vein by the 9th week (Figs. 2 and 3). He was discharged 3 weeks later. At the last follow-up visit, approximately 3½ years after injury, the portal vein was demonstrated to be normal on ultrasonographic examination. In the second patient, who had a pancreatoduodenectomy and portal vein and vena caval repair, ultrasonographic examination 2 and 5 weeks after the procedure proved the veins to be patent (Fig. 4). The third patient was a 17-year-old woman who had sustained injuries to the portal vein, abdominal aorta, and the renal vein. During an uneventful recovery

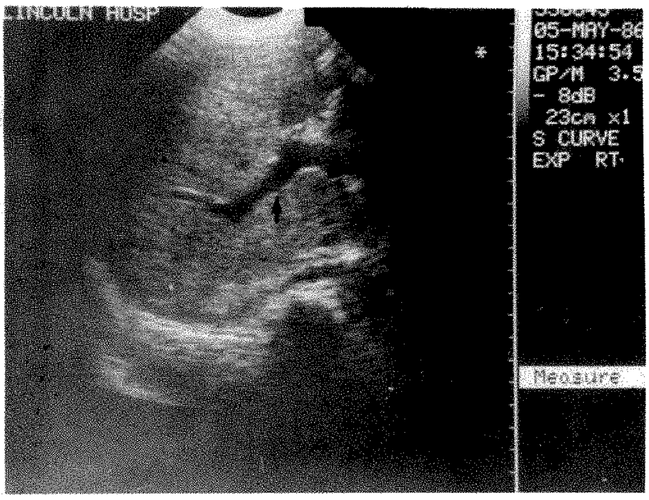

FIG. 3. Left oblique parasaggittal view 3½ years later: portal vein (arrow) completely normal.

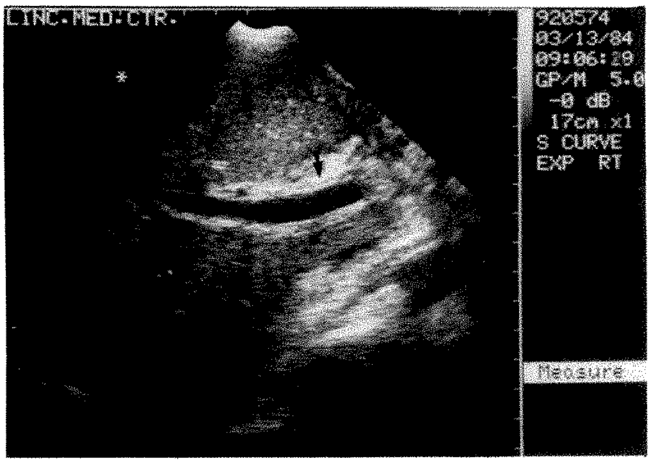

FIG. 4. Patient 2. Left oblique parasaggittal view 5 weeks after repair, showing patent portal vein (arrow).

from the repair of these injuries, ultrasonographic examination on the 10th day after operation established patency of the repaired portal vein (Fig. 5).

Discussion

The experience with portal vein trauma of each of several busy trauma centers is limited to fewer than 50 patients collected over several decades. Stone et al.,[10] for example, could find only 46 patients during a 23-year period. Despite this rarity, these lesions are of concern to the trauma surgeon because of their potentially lethal nature and the anatomic and physiologic importance of the portal vein.

The portal vein provides as much as 80% of the metabolic and oxygen needs of the liver and is the principal conduit for visceral efferent flow. The concealed location of the portal vein in the portal triad protects it from injury but presents numerous difficulties to adequate exposure and control. The frequent presence of concomitant injuries to other major vessels and organs contributes to massive blood loss. All of our patients presented with severe hypotension, and 57% of the patients had additional vascular injuries. Five (35%) were *in extremis* on admission, and each of four of them had a resuscitative thoracotomy and aortic occlusion before an attempt was made to control hemorrhage. As shown in this report and several others,[3-12] these factors contribute to a high mortality rate. Death occurred in 22 of the reported patients before the portal vein could be controlled.

The technical details of exposure of the portal vein and its tributaries are reviewed by Petersen et al.,[7] Stone et al.,[10] and, more recently, Sheldon et al.[12] and consist of mobilization of the right colon and small bowel mesentery as well as the pancreas and the splenic vein to provide access to the posterior aspect of the portal vein. Occasionally, division of the pancreatic neck may be the only feasible approach to the retropancreatic confluence of the splenic and superior mesenteric veins.[7] Packing, vascular clamps, and the Pringle maneuver are useful in temporarily staunching exsanguinating hemorrhage from the portal vein while other major vascular lesions are receiving attention.

Lateral venorrhaphy has been the preferred surgical approach and yields a significant survival rate (Table 2). In a few instances, an end-to-end anastomosis may be accomplished. For patients with injuries precluding portal vein reconstruction, portasystemic shunt has been proposed. However, the potential complication of hepatic encephalopathy and the inadvisability of per-

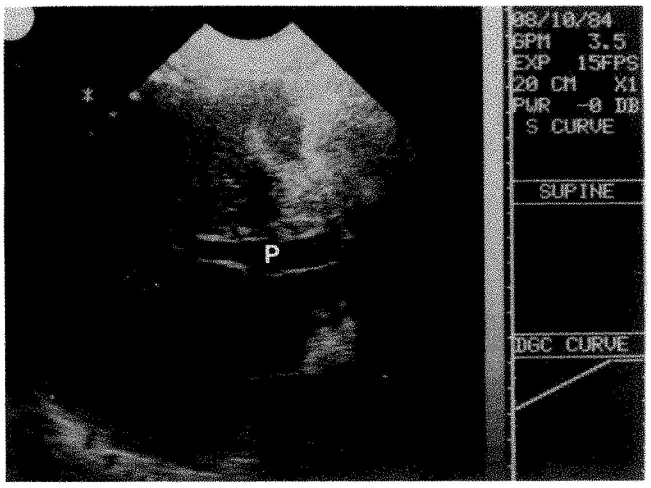

FIG. 5. Patient 3. Left oblique parasaggittal view 10 days after repair, demonstrating patent portal vein (P).

TABLE 2. *Management Methods in Reported Studies of Portal Vein Injuries**

Study	Repair	Ligation	Death before Repair	Others†	Total
Patton and Johnston, 1960[1]	2 (2)	—	—	—	2 (2)
Fish, 1966[2]	2 (1)	—	—	—	2 (1)
Chisolm and Lenio 1972[3]	1 (1)	2 (1)	—	—	3 (2)
Bostwick and Stone 1976[5]‡					24 (6)
Mattox et al., 1975[4]§					22 (11)
Graham et al., 1978[6]§	26 (16)	4 (0)	5 (0)	2 (2)	37 (18)
Pachter et al., 1979[8]	—	1 (1)	—	—	1 (1)
Petersen et al., 1979[7]‖	19 (13)	5 (3)	3 (0)	1 (1)	28 (17)
Busuttil et al., 1980[9]	4 (3)	1 (0)	2 (0)	3 (2)	10 (5)
Stone et al., 1982[10]‡	17 (12)	18 (9)	7 (0)	4 (1)	46 (22)
Kashuk et al., 1982‖	8 (3)	1 (0)	—	—	9 (3)
Wiencek and Wilson, 1986[13]	12 (6)	3 (0)	2 (0)	—	17 (6)
Sheldon et al., 1985[12]‖					29 (?)
This study	10 (6)	1 (1)	3 (0)	—	14 (7)
Total	101 (62)	36 (15)	22 (0)	10 (6)	169 (84), 50%

* Number of survivors in parentheses.

† End-to-end anastomosis 5 (2); portasystemic shunt 2 (1); vein graft 3 (3).

‡·§·‖ Some of the reports of patients in these studies were duplicated in subsequent reports from the same insitution.

forming such a technically involved operation in a patient with an unstable condition argue against such a procedure. In his collective review of the literature in 1966, Fish[2] noted that encephalopathy developed in four of five patients treated by primary portacaval shunt. Other maneuvers, such as a saphenous vein interposition graft to the portal vein, have been employed sporadically (Table 2). Ligation of the traumatized portal vein is the other major option in management.

The Role of Ligation

After the initial observations of Child et al.[15] that ligation of the portal vein was compatible with survival, this procedure found increasing favor. Pachter et al.[8] reviewed 10 cases from the literature with five survivors and added another successful case of their own. In a more recent review, Stone et al.[10] presented a survival rate of 80% with planned ligation of the vein. A 2- to 36-month follow-up with angiography in five of the survivors of ligation showed excellent collateral flow to the liver and no evidence of portal hypertension. Similarly, a favorable survival rate was noted by Petersen et al.[7] Even though one of their patients had an elevated portal pressure level after ligation of the vein, none had esophageal varices develop. It is recommended, however, that these patients be subjected to a "second-look" operation 24 hours later to detect small bowel infarction from portal hypertension.[7,8,12]

TABLE 3. *Reported Follow-up after Portal Venorrhaphy or Ligation*

Study	N	
Patton and Johnston, 1960[1]	2	Portal vein thrombosis at laparotomy
Fish, 1966[2]	1	Portal vein thrombosis at laparotomy
Pachter et al., 1979[8]	1	Reconstitution of portal vein after ligation on angiographic examination
Stone et al., 1982[10]	5	Excellent collateral flow after ligation on angiographic examination
Ivatury et al., 1985[22]	1	Portal vein thrombosis on ultrasonographic examination

The Fate of the Repaired Portal Vein

Although ligation is an acceptable option in the management of an unreconstructable portal vein laceration in the patient with an unstable condition, and although lateral venorrhaphy is the preferred mode of treatment, a relevant concern is the patency rate after repair. Unfortunately, this issue has not been addressed adequately in the surgical literature. Stone[14] and Petersen et al.[7] commented on the low patency of the portal vein after repair but did not provide specific data as to the number of patients studied *versus* the number of patent veins. In other large studies of portal vein trauma,[4,6,12] follow-up studies of the repaired veins were not provided. As indicated in Table 3, data regarding the status of the portal venous circulation after repair are available in only 10 of the 169 patients described in the literature. Seven of these patients had ligation of the portal vein.

The complication of postvenorrhaphy thrombosis of the portal vein is not without significant sequelae. Patton and Johnston[1] recorded instances of portal hypertension with variceal bleeding secondary to portal vein thrombosis. Fish[2] and Chisolm and Lenio[3] reported deaths resulting from this complication. Stone et al.[10,14]

and Pachter et al.[8] emphasized the gravity of splanchnic pooling secondary to portal thrombosis. The resultant excessive sequestration of intravascular fluid may cause hypovolemia and hypotension. Precise hemodynamic monitoring becomes essential. It seems desirable, therefore, to study the portal vein after repair. However, the difficulty and the potential complications of performing invasive studies, such as selective angiographic examination, in a critically ill patient may outweigh the possible benefits from such studies. A noninvasive, easily reproducible investigation would circumvent these problems and may prove beneficial in the postoperative management. In our experience, ultrasonography has fulfilled these criteria. Further support for this approach may be obtained by examining the role of ultrasonography in nontraumatic conditions of the portal vein.

Ultrasonography in the Evaluation of the Portal System

The normal portal vein has been recognized as an important landmark in upper abdominal ultrasonography. Merritt[16] studied the portal vein in 100 randomly selected examinations and identified it in 97% of the cases as it entered the porta hepatis, in 83% as it crossed the inferior vena cava, and in 83% at its origin. In addition, he documented the important ultrasonographic findings of portal vein thrombosis in three patients in whom angiographic examination subsequently confirmed this process. Raskin et al.[17] diagnosed portal and hepatic vein thrombosis by ultrasonographic examination. Webb et al.[18] documented the reliability of ultrasonography in assessing the patency of the portal vein in 20 patients with angiographic evidence of extrahepatic vein thrombosis. Employing real-time gray-scale ultrasonography, Weinreb et al.[19] presented a standard chart of normal portal vein measurements in 148 patients. Furthermore, they successfully used "sonographic portography" to screen patients with cystic fibrosis for the onset and progress of portal hypertension. In a more recent communication, Van Gansbeke et al.[20] demonstrated the reliability of real-time ultrasonography in the detection of portal thrombosis. They also pointed out that the detection of multiple serpiginous periportal collaterals with inability to image the normal portal vein is important evidence of portal vein obstruction. These observations may find an application in the sequential study of the patient treated by portal vein ligation. Finally, the more sophisticated Duplex ultrasonography is capable of measuring quantitative flow of the normal portal system and the system with portasystemic shunts. Using this technique, Ackroyd et al.[21] were able to measure portal flow in normal subjects and in patients with portasystemic shunts.

It is evident that ultrasonography provides a versatile, noninvasive, and reliable method for investigating the portal system. Our data suggest that this modality may have an important application for the assessment of patency after portal vein reconstruction. In our first patient it facilitated an early diagnosis of portal vein thrombosis and enabled a serial follow-up while the patient was treated by anticoagulation therapy. In the other two patients, the portal vein could be identified and the patency of the repair could be documented. In patients treated by ligation of the portal vein, sequential ultrasonography may be of value in monitoring the development of collateral channels as well as portal hypertension, should it occur. Wider application of this noninvasive modality will, perhaps, enhance our understanding of the sequelae of venorrhaphy and ligation of the injured portal vein.

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Survival after Trauma in Geriatric Patients

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In contrast to other studies, a recent report from the authors' institution has shown a good prognosis for functional recovery in geriatric patients that survive trauma. Because most survivors regained their pre-injury function, the authors examined factors related to nonsurvival in this population of 82 consecutive blunt trauma victims older than the age of 65. Seventeen patients died (21%). Compared with survivors, nonsurvivors were older, had more severe overall injury, and had more severe head and neck trauma but did not differ in severity of trauma that did not involve the head and neck, number of body regions injured, mechanism of injury, or incidence of surgery after injury. Nonsurvivors experienced more frequent complications (82% *vs.* 33%, $p < 0.05$), including a higher incidence of cardiac complications (53% *vs.* 15%, $p < 0.05$) and ventilator dependence for 5 or more days (41% *vs.* 14%, $p < 0.05$). Mortality rates were increased in patients who were 80 years of age or older compared with those ages 65–79 (46% *vs.* 10%, $p < 0.01$), despite injury of similar severity. More frequent complications may contribute to an increased mortality rate in the older group, including an increased incidence of prolonged mechanical ventilation (36% *vs.* 12%, $p < 0.025$), cardiac complications (54% *vs.* 10%, $p < 0.01$), and pneumonia (36% *vs.* 16%, $p < 0.06$). Severely injured patients (Injury Severity Score [ISS] ≥ 25) older than 80 years old had a mortality rate of 80%, and the survivors required permanent nursing home care. Discriminant analysis yielded a reliable method of differentiating survivors from nonsurvivors based on age, ISS, and the presence of cardiac and septic complications. To assess the accuracy of the discriminant function, 61 consecutive patients admitted during 1985 were reviewed prospectively. Discriminant scoring predicted outcome correctly in 92% of these patients. A Geriatric Trauma Survival Score (GTSS) based on the discriminant function was calculated for each of the 143 patients studied and was highly correlated with mortality rate ($r = 0.99$, $p < 0.001$). Thus, the GTSS may serve as a valuable tool for evaluating death in geriatric trauma victims. Furthermore, because complications are potentially avoidable and contribute to increased mortality rates, routine aggressive care for geriatric patients with moderate overall injury is indicated.

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ALTHOUGH the elderly population is growing, few studies have examined the outcome of seriously injured elderly patients. Oreskovich et al.[1] suggested that aggressive care of these patients is futile because of a high mortality rate and the finding that survivors rarely regained their pre-injury function. In contrast, we have recently reported a favorable prognosis for functional recovery in 63 consecutive geriatric patients with trauma.[2] Clearly, further studies to define factors related to mortality rate and outcome are required before aggressive care of any geriatric patient with trauma is withheld. Because most of our survivors were able to return home, we have now studied factors related to nonsurvival in this population. Our goals were as follows: (1) to determine any factors that predicted that resuscitation would be futile; and (2) to assess the impact of potentially avoidable complications on mortality rate.

Methods

We reviewed the records of 82 consecutive patients older than age 65 admitted to the Rhode Island Hospital Trauma Service from September 1982 to December 1984. All patients with thermal, penetrating, or isolated orthopedic injury were excluded. An Injury Severity Score (ISS)[3,4] based on the 1985 revision of the Abbreviated Injury Scale (AIS)[5] was calculated for each patient and confirmed by the analysis of a second, blinded observer. The AIS values for head and neck, thorax, abdo-

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men, and extremity trauma were also recorded. The age, sex, mechanism of injury, number of body regions injured, presence of pre-injury cardiopulmonary disease, and length of hospital stay were noted for each patient. Those patients who required surgery after injury were grouped into emergent (less than 24 hours after admission) and delayed surgery groups. The type of surgery required was also recorded.

Cardiac, pulmonary, and septic complications and the number of complications during each patient's hospitalization were noted. Cardiac complications included myocardial infarction, arrhythmia with hypotension, and unstable or recent-onset angina. Pulmonary complications included pneumonia and ventilator dependence for 5 days or longer. The diagnosis of sepsis required blood cultures with positive results in the presence of a characteristic hemodynamic profile.

Data are presented as mean plus or minus standard error. Characteristics of survivors and nonsurvivors were compared by the chi square test and analysis of variance with comparison of individual means by use of Newman-Keuls testing.[6] A multivariate discriminant analysis using SPSS-X[7] (Brown University Computer, IBM VM/CMS 3081D) was used to identify variables that differentiated survivors from nonsurvivors. A stepwise model was used wherein variables were sequentially selected to enter the analysis. The order of selection was such that the residual variance in the population was minimized with the addition of each variable.[8]

In order to assess the predictive value of the discriminant analysis, we tested the ability of the function to predict outcome in a second population of geriatric trauma victims (test population). We prospectively reviewed 61 additional patients admitted from January through December 1985. The discriminant score calculated for each individual test case was used to assign it to the group (survivor or nonsurvivor) for which its probability of membership was greatest. The percentage of patients classified correctly (*i.e.*, predicted and actual outcome identical) was taken as an estimate of the predictive value of the discriminant function.

Results

Geriatric Population

TABLE 1. *Characteristics of 82 Geriatric Trauma Victims*

Age (years)	75.8 ± 0.8
Sex	54 M/28 F
Mechanism of injury	39 falls, 40 MVAs, 3 assaults
Injury Severity Score	17.9 ± 1.2
Abbreviated Injury Scale	
Head and neck	2.4 ± 0.2
Thorax	1.4 ± 0.2
Abdomen	0.7 ± 0.1
Extremities	0.9 ± 0.1
BRI	
Head and neck	52 (63%)
Thorax	40 (49%)
Abdomen	24 (29%)
Extremities	33 (40%)
Number of BRI	1.8 ± 0.1
Stay (days)	24.4 ± 2.5
Complications	
Number per patient	0.8 ± 0.1
Cardiac	19 (23%)
Pneumonia	18 (22%)
Vent ≥ 5 days	16 (20%)
Sepsis	5 (6%)

M = male; F = female; MVA = motor vehicle accident; BRI = body regions injured.

The characteristics of the population are provided in Table 1. The population had a mean age of 75.8 ± 0.8 years and a moderate overall level of injury with a mean ISS of 17.9 ± 1.2. All patients had blunt injury secondary to falls (48%), motor vehicle accidents (33%), pedestrian–motor vehicle accidents (16%), or assault (4%). Men outnumbered women nearly 2:1. Twenty-three patients (28%) had an ISS of 25 or more. The head and neck region was most frequently injured (64%), and 49 patients (60%) had multiple body regions injured. Most patients had pre-injury cardiac or pulmonary disease (72%). Half of the patients required surgery after trauma, and surgery was emergent in two-thirds of these cases. The types of operations performed are listed in Table 2.

Complications developed in 35 patients (43%), with a mean number of complications per patient of 0.8 ± 0.1. Cardiac complications (23%) and pneumonia (22%) were most frequent. Sixteen patients (20%) required assisted mechanical ventilation for 5 days or longer. Systemic sepsis occurred in only five patients (6%). More than one complication developed in 18 patients (22%) which included 11 with prolonged ventilatory assistance and pneumonia.

Seventeen patients died during hospitalization, yielding a mortality rate of 21%. Table 3 depicts the characteristics of survivors and nonsurvivors. Nonsurvivors were older (81.7 ± 2.1 *vs.* 74.3 ± 0.8 years, $p < 0.001$), had more severe overall injury (ISS: 26.7 ± 2.8 *vs.* 15.8 ± 1.1, $p < 0.001$), and had more severe head and neck

TABLE 2. *Surgery in 82 Geriatric Trauma Victims*

	No. of Patients
Surgery	42 (51%)
Emergent	29 (69%)
Delayed	13 (31%)
Type of operations performed	
Central nervous system	18 (43%)
Abdomen	9 (21%)
Orthopedic	10 (24%)
Thorax	2 (5%)

TABLE 3. *Comparison of Survivors and Nonsurvivors*

	Survivors (N = 65)	Nonsurvivors (N = 17)	
Age	74.3 ± 0.8	81.7 ± 2.1	*
Sex	44 M/21 F	10 M/7 F	NS†
Mechanism of injury	31 falls/31 at MVAs/3 assaults	8 falls/9 MVAs	NS†
ISS	15.8 ± 1.1	26.7 ± 2.8	*
AIS			
Head and neck	2.1 ± 0.2	3.5 ± 0.5	‡
Thorax	1.3 ± 0.2	1.6 ± 0.5	NS†
Abdomen	0.8 ± 0.2	0.4 ± 0.2	NS†
Extremities	0.9 ± 0.2	1.0 ± 0.3	NS†
Number of BRI	1.8 ± 0.1	1.8 ± 0.2	NS†
Stay (days)	25.2 ± 2.5	21.5 ± 7.6	NS†
Complications			
Number per patient	0.6 ± 0.1	1.8 ± 0.3	‡
Cardiac	10 (15%)	9 (53%)	‡
Pneumonia	12 (19%)	6 (35%)	NS†
Vent ≥ 5 days	9 (15%)	7 (41%)	‡
Sepsis	2 (3%)	3 (18%)	NS†

* $p < 0.01$.

† NS = not significant, $p > 0.05$.

‡ $p < 0.05$.

MVA = motor vehicle accident; BRI = body regions injured; M = male; F = female.

trauma (AIS: 3.5 ± 0.5 *vs.* 2.1 ± 0.2, $p < 0.025$). There was no difference in AIS values between survivors and nonsurvivors for trauma that did not involve the head and neck, number of body regions injured, mechanism of injury, incidence of surgery (emergent or delayed), or length of hospital stay.

TABLE 4. *Comparison of Patients Ages 65 to 79 with Patients 80 Years Old and Older*

	Ages 66–79 (N = 58)	Age ≥ 80 (N = 24)	
Sex	15 M/9 F	39 M/19 F	NS*
Mechanism of injury	30 falls/25 MVAs/3 assaults	9 falls/15 MVAs	NS*
Injury Severity Score	17.4 ± 1.3	19.3 ± 2.5	NS*
Abbreviated Injury Scale			
Head and neck	2.2 ± 0.3	2.8 ± 0.4	NS*
Thorax	1.5 ± 0.2	1.0 ± 0.3	NS*
Abdomen	0.8 ± 0.2	0.5 ± 0.2	NS*
Extremities	0.9 ± 0.2	1.0 ± 0.3	NS*
Number of BRI	1.9 ± 0.1	1.7 ± 0.1	NS*
Stay (days)	23 ± 2.9	27.9 ± 4.7	NS*
Complications			
Number per patient	0.6 ± 0.1	1.5 ± 0.3	†
Cardiac	6 (10%)	13 (54%)	†
Pneumonia	9 (16%)	9 (36%)	NS*
Ventilator ≥ 5 days	7 (12%)	9 (36%)	†
Sepsis	3 (5%)	2 (8%)	†
Mortality rate	10%	46%	‡

* NS = not significant, $p > 0.05$.

† $p < 0.05$.

‡ $p < 0.01$.

BRI = body regions injured; M = male; F = female; MVA = motor vehicle accidents.

Complications were more frequent in nonsurvivors. Complications developed in 82% of nonsurvivors compared with 33% of the survivors ($p < 0.05$). Nonsurvivors had a higher incidence of cardiac complications (53% *vs.* 15%, $p < 0.05$) and ventilator dependence for 5 or more days (41% *vs.* 14%, $p < 0.05$). Four of 11 patients (36%) with the combination of pneumonia and assisted ventilation for 5 or more days died.

If mortality rate after trauma in geriatric patients is indeed primarily related to advanced age, patients older than 80 years may be at increased risk. Twenty-four patients (29%) were 80 years or older. The mortality rate in this age group was more than fourfold greater than for patients ages 65 to 79 (46% *vs.* 10%, $p < 0.01$, see Table 4). There was no difference in number of body regions injured, ISSs, AIS values for any body region, or length of hospital stay between these two age groups. However, there were more complications in patients who were 80 years and older (1.8 ± 0.3 *vs.* 0.6 ± 0.1, $p < 0.001$). In the older group prolonged mechanical ventilation (36% *vs.* 12%, $p < 0.025$) and cardiac complications (54% *vs.* 10%, $p < 0.01$) were more frequent and there was a trend toward a higher incidence of pneumonia (36% *vs.* 16%, $p < 0.06$). Thus, advanced age or more frequent complications may contribute to an increased mortality rate in patients older than 80 years old, although injury severity was not greater. However, severe overall injury in the older group appears to denote a particularly poor prognosis. Of 10 patients older than age 80 with ISSs greater than or equal to 25, eight died and the two survivors required permanent nursing home care.

Discriminant Analysis

Discriminant analysis revealed that outcome was related to four variables: ISS, age, and the presence of cardiac (CARDIAC) or septic (SEPSIS) complications (0 = no complication, 1 = complication) *via* the following discriminant function:

$$\text{Discriminant score} = (0.086)\text{AGE}$$

$$+ (0.064)\text{ISS} + (1.49)\text{SEPSIS} + (1.06)\text{CARDIAC} - 7.96$$

The canonic correlation coefficient was 0.63 ($p < 0.001$). Survivors had a mean discriminant score of −0.4, whereas nonsurvivors had a mean score of 1.55. Classification of each individual case based on its probability of group membership, as if survival were unknown, revealed that 85% of the cases were correctly classified by the discriminant function (Table 5). This percentage was not increased significantly if other variables were added to the discriminant analysis.

Test Population

To test the accuracy of the discriminant function, we prospectively reviewed the cases of 61 additional consecutive blunt trauma victims older than the age of 65

TABLE 5. *Analysis of the Predictive Value of the Discriminant Function: Predicted Outcome (Based on the Discriminant) was Compared with the Actual Outcome for the 82 Patients in the Original Population and for the 61 Patients in the Test Population**

	Predicted Survival	Predicted Death
Original patients (N = 82)		
Actual		
Survival	54	11
Death	1	16
Test population (N = 61)		
Actual		
Survival	50	1
Death	4	6

* Overall, 85% of the original patients were classified correctly by the discriminant function. In the test population, 92% were correctly classified.

admitted to our Trauma Service during the 1985 calender year. The characteristics of the test population are listed in Table 6. The mean age and incidence of cardiac complications and sepsis in the test population were similar to those of the original population. The mean ISS and mortality rate were somewhat lower, however. Despite these differences in the test population's characteristics, the discriminant function predicted outcome correctly in 92% of the test cases (Table 5).

Geriatric Trauma Survival Score and Mortality

Most errors in classification of individual cases as survivors or nonsurvivors occurred in patients with discriminant scores in the middle range (*i.e.*, discriminant score between 0 and 1.5). The mortality rate for patients scoring in this range is significantly less than 100% and greater than zero (Fig. 1). Because the mortality rate associated with each discriminant value in the test population was strikingly similar to the respective mortality rate in the original population (Fig. 1), we combined the two groups in an attempt to derive a clinically useful formula for assessing the mortality rate of geriatric patients with trauma admitted to our institution. First, we performed an algebraic transformation of the original discriminant function to obtain a Geriatric Trauma Survival Score (GTSS):

$$\text{GTSS} = 0.9(\text{AGE} - 65) + 0.6(\text{ISS}) + 14.9(\text{SEPSIS}) + 10.6(\text{CARDIAC})$$

As in the discriminant formula, SEPSIS and CARDIAC refer to the presence or absence (score = 1 or 0, respectively) of septic and cardiac complications. The GTSS differs from the original discriminant function in that all values are greater than zero. The range of possible GTSSs includes a minimum score near zero. Although the theoretic maximum GTSS is greater than 100, this would require extreme age and an ISS near the maximum possible score of 75. The calculated GTSSs in the 143 patients studied ranged from 3.9 to 58.4, with a mean GTSS of 21.7 ± 12.4 (standard deviation [SD]). The mean GTSS for survivors was 18 ± 9.5 (SD) and for nonsurvivors 37.8 ± 2 (SD).

TABLE 6. *Characteristics of the 61 Prospectively Reviewed Geriatric Patients with Trauma Constituting the Test Population*

Age (years)	76.3 ± 0.9
Injury Severity Score	10.0 ± 0.9
Complications	
Cardiac	15%
Sepsis	3.3%
Mortality rate	16%

Having derived a GTSS that is easier to calculate than the original discriminant function, we examined the mortality rate associated with values of the GTSS. The GTSS values for all patients were ranked in ascending order and arbitrarily divided into 15 roughly equal subgroups with consecutive scores. The mean GTSS and mortality rate for each subgroup were determined and plotted (Fig. 2). An iterative least-square logistic curve fitting model[9,10] was used to determine the best curve relating GTSS and mortality rate. In order to provide an accurate assessment of the curve, we assumed that patients with a near-maximum GTSS of 100 had a mortality rate of 100%. Thus, the asymptote of the curve converged on a 100% mortality rate for high GTSSs. This assumption appears reasonable, because a GTSS of 100 requires a near-maximum ISS and the mortality rate in younger patients with injury of this severity approaches 100%. The best fit relationship was:

$$\text{Mortality (\%)} = 100 - 100/(1 + [\text{GTSS}/32.8]^{5.2})$$

The correlation coefficient for the curve fit by the above formula was 0.99 ($p < 0.001$). The GTSS associated with

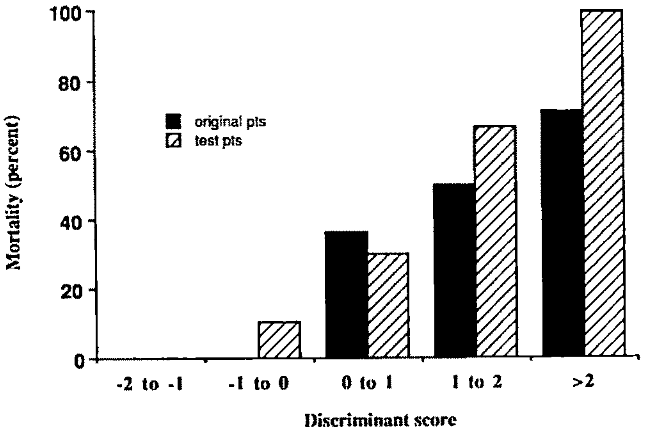

FIG. 1. Mortality rate associated with increasing values of the discriminant score. The mortality rates of patients in the original and test populations for a given discriminant score were similar. Most errors in classification of patients as survivors or nonsurvivors were in cases with discriminant scores in the middle range.

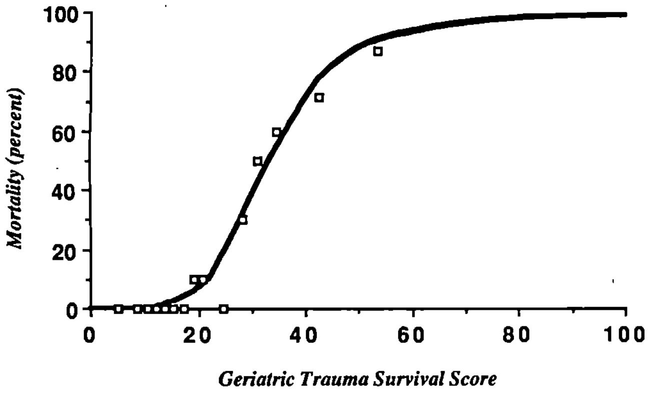

FIG. 2. Mortality rate associated with increasing values of the GTSS in the total population of 143 patients. There was a strong correlation between GTSS and mortality rate ($r = 0.99$, $p < 0.001$) with the use of the least-squares logistic analysis. A GTSS of 32.8 led to a predicted mortality rate of 50%, and the mortality rate of patients with GTSSs greater than or equal to 50 was 89%.

a 50% mortality rate was 32.8, with a 20% mortality rate was 25.5, and with an 80% mortality rate was 43.7. The curve predicts a 95% mortality rate for patients with a GTSS of 62.8.

Discussion

Elderly persons are seriously injured less frequently than any other segment of the population.[11] However, the mortality rate of elderly patients after trauma is higher than for any other age group.[11,12] Despite their lower injury rate, the elderly patients consume nearly one-third of all health care resources expended on trauma care.[13] Furthermore, the geriatric segment of the population is growing rapidly. The elderly population is projected to increase by 18% over the next 10 years[14] and by more than 50% within 50 years.[15] Clearly, trauma in elderly patients will become an increasingly important health care issue in the future.

Few studies have examined why the mortality rate is increased in geriatric patients after trauma.[1,16] Furthermore, comparison of such studies is potentially difficult. Many injured elderly persons have relatively minor trauma (*i.e.*, hip fractures resulting from falls), and high morbidity and mortality rates have been reported in this situation, presumably as a result of severe intrinsic disease.[17,18] Including these debilitated patients in a study of trauma would inevitably bias the outcome. Because we were primarily interested in previously healthy, independent patients with major trauma,[1,16] we defined our population carefully. We included only patients admitted to the trauma service and excluded those with isolated orthopedic injuries. Because nearly all of our patients were living independently before injury,[2] these criteria probably excluded most debilitated patients. Thus, we feel the study population is representative of previously independent elderly persons admitted to most trauma centers.

The mortality rate in our patients was high despite moderately severe injuries. In one of the few previous studies that has examined factors related to mortality rate in geriatric patients, Oreskovich et al.[1] in Seattle reported that nonsurvivors had an increased frequency of head trauma and thermal injury. However, they found no difference in age or injury severity as measured by ISS between patients that survived and those that died. In contrast, our data suggest that both of these factors contribute to mortality rate. The reasons underlying these conflicting results are unclear. A possible explanation may be found in the revisions of the ISS since its introduction in 1976. We used the 1985 revision of the ISS[5] that includes physiologic modifications added after the original version used by Oreskovich et al.[1] Thus, the updated ISS may be more useful than previous versions in predicting mortality rate.

In the Seattle study,[1] most nonsurvivors were characterized by hypotension upon arrival, prehospital intubation, prolonged mechanical ventilation, and pulmonary sepsis. However, this nonsurvivor profile is difficult to interpret, because the mortality rate associated with each factor was not reported. For example, although all nonsurvivors required prolonged ventilatory assistance, the overall mortality rate of patients in whom this complication developed was not reported. In our series, 44% of patients requiring prolonged ventilatory assistance died and six of nine that survived eventually returned home after hospital discharge.[2] Clearly, the need for prolonged ventilatory assistance is not an indication for withdrawing support.

Mortality rate in geriatric patients with trauma is difficult to predict based solely on the ISS.[12] Oreskovich et al.[1] found no difference in ISSs between survivors and nonsurvivors. Although our nonsurvivors had a higher ISS than survivors and ISS was correlated with outcome, the ISS alone was a poor predictor of survival rate. For this reason, we used a multivariate analysis to determine factors related to mortality rate. Discriminant analysis determined that survival rate was primarily related to age, ISS, and the presence of cardiac or septic complications in the original population, and the importance of these factors was confirmed in 61 additional prospectively reviewed patients. Algebraic transformation of the discriminant function yielded a Geriatric Trauma Survival Score, or GTSS, that was easier to calculate than the original equation.

Although the GTSS was strongly related to mortality rate, its clinical utility is difficult to determine. The GTSS appears to be a good predictor of mortality rate in geriatric patients at our institution, but its predictive value for other institutions has not been tested. Clearly, the GTSS should not be used to predict the mortality rate of geriatric trauma victims or the futility of resuscitation because the number of patients with high GTSS values in our study was small. Furthermore, the GTSS is unlikely to be helpful in determining whether or not resuscitation of an elderly patient in the emergency room should be continued, because complications, which are important contributors to the GTSS, are often not early events. In this study we have not examined prehospital variables (*i.e.*, prehospitalization endotracheal intubation, hypotension on arrival, *etc.*): doing so may have increased the predictive value of the GTSS.

The futility of geriatric trauma care is not supported by our data. Although the small group of patients with GTSSs over 50 had a high mortality rate, it is clear that further study is required before aggressive care of these patients is deemed hopeless. At the present time, the GTSS is likely to be most useful for trauma centers to evaluate their own experience with geriatric patients and for comparing the results of different institutions. The GTSS may also be useful for evaluating the effect of changes in treatment protocol at an individual institution. For example, routine invasive cardiac monitoring for patients with trauma who are older than 80 years old may decrease the mortality rate associated with cardiac complications and shift the curve relating GTSS to mortality rate to the right.

The data demonstrate the important role of complications in deaths of geriatric trauma victims. Cardiac complications in particular may reflect the severity of underlying disease, and many authors have suggested that the mortality rate is difficult to predict in this population because of intrinsic disease that may be clinically silent before injury.[1,12] Interestingly, the presence of previously diagnosed cardiopulmonary disease was not related to mortality rate. Thus, the lack of significant medical history should not be used as a criterion for intensive care unit admission and invasive monitoring in patients with moderate overall injury. Notably, of the factors related to survival determined by discriminant analysis, only the complications might be avoided with more aggressive care. Routine aggressive treatment of geriatric trauma victims, including intensive care unit admission, early invasive cardiac monitoring, and aggressive pulmonary therapy, might prevent complications in these patients and decrease mortality rates. Thus, our data indicate that routine aggressive care for elderly patients with moderate overall injury is appropriate, particularly because the survivors had a good prognosis for functional recovery.[2]

In summary, our data suggest that geriatric patients with trauma who are older than 80 years old, have severe overall injury (ISS $\geq$ 25), or have severe head and neck trauma have an increased mortality rate. Nearly half of the patients older than the age of 80 died after trauma, with no increase in injury severity in this group. The mortality rate is also increased in patients with complications, particularly cardiac complications and ventilator dependence. Cardiac and pulmonary complications were more frequent in patients who were older than 80 and this may contribute to the increased mortality rate in this group. Patients older than the age of 80 who had severe overall injury and patients with GTSSs greater than or equal to 50 had an extremely poor prognosis. Aggressive care of patients in this group may be futile, but further study is required to confirm this result. Because complications are potentially avoidable and contribute to increased mortality rates, routine aggressive care for geriatric patients with moderate overall injury is indicated.

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Adrenergic Control of Adipocyte Lipolysis in Trauma and Sepsis

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Adipocyte lipolysis and its adrenergic control were studied *in vitro* from normal patients and those with trauma and sepsis. The adrenergic receptors were studied in terms of their responsiveness, a measure of the postreceptor mechanism, and their sensitivity, a measure of the receptor number or affinity. With early trauma, beta-adrenergic responsiveness and receptor number were significantly decreased. This is desensitization of the beta-receptors with down regulation and indicates increased *in vivo* lipolysis in early injury. After 4 days these changes had returned to normal. Early sepsis resulted in a significant increase in beta- and alpha-receptor responsiveness with beta-upregulation. This indicated hypersensitivity of the adipocyte adrenergic receptors and suggests the presence of an *in vivo* block of the adrenergic receptors in early sepsis. This would decrease adipocyte lipolysis. After 4 days there was a decrease in beta-receptor responsiveness in the patients with sepsis, indicating that the adrenergic receptor block was no longer present and adipocyte adrenergic stimulated lipolysis was increased.

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THE INJURED OR SEPTIC PATIENT has an elevated metabolic rate.[1-3] The fuel for this increased energy demand is a mixture of protein, fat, and carbohydrate; however, present data suggest that lipid calories provide the major calorie source.[4,5] These calories are stored as triglycerides in the adipocyte and are mobilized at the time of increased demand. Although this appears straightforward for the patient with trauma, alterations in lipid metabolism have previously been demonstrated in sepsis. Hepatic use of fat is impaired in sepsis and may contribute to the development of the fatty infiltration of the liver.[6] In patients with sepsis, lipid use and oxidation may be decreased, and this is possibly related to decreased clearance by the liver. There has been documentation of increased levels of plasma free fatty acids (FFAs) and plasma triglyceride levels in patients with severe sepsis.[7] Other studies have reported decreased plasma FFA levels in sepsis.[6,9] Previous studies from our laboratories using a ^{14}C-palmitate infusion and indirect calorimetry have documented an increase in total body lipid clearance with an increase in lipid oxidation in patients with both trauma and sepsis.[4,5] Subsequent studies on lipoprotein lipase (LPL) activity in the patient with trauma and sepsis showed a significant difference *in vitro.* The LPL activity was decreased in the patient with sepsis and increased in the injured patient. The decreased activity of both the adipose and muscle LPL in the patient with sepsis suggests a defect in clearance of the lipoproteins, particularly in those patients who were hypertriglyceridemic. In addition, the study showed that the direct relationship of insulin to LPL activity was lost in the patient with sepsis.[8] Thus, fat metabolism is still unclear in the injured patient, particularly in the patient with sepsis.

Lipolysis of the stored triglycerides and the control of adipocyte lipolysis is important in mobilization of lipid in the injured patient. Lipolysis in the adipocyte is carried out by the enzyme hormone sensitive lipase (HSL).[10] This enzyme complex is controlled by a number of circulating hormones, including the catechol-

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TABLE 1. *Patient Characteristics*

Patients with Trauma			Patients with Sepsis			
Age	Sex	Diagnosis	Age	Sex	Diagnosis	Organism
22	M	Gunshot wound to sigmoid colon	62	F	Pyelonephritis	*Escherichia coli*
30	M	Multiple fractures	40	F	Cathetar sepsis	*Staphylococcus aureus*
50	M	Multiple fractures and pulmonary contusion	56	M	Diverticulitis	*E. coli*
19	M	Gunshot wounds left chest and left lung	20	M	Appendiceal abscess	Enterococcus, *Bacteroides fragilis*
33	M	Gunshot wound to right lobe liver	24	M	Fecal peritonitis	*E. coli, B. fragilis*
			55	M	Cholangitis	*E. coli*
			66	M	Fecal peritonitis	*E. coli, B. fragilis*
			72	M	Subphrenic abscess	*E. coli, B. fragilis*
			67	F	Fecal periotonitis	*E. coli,* Proteus
			51	M	Fecal peritonitis	*E. coli*

amines. Presently it appears that HSL is stimulated by beta-1-adrenergic receptors and inhibited by alpha-2-receptors in the human adipocyte. The role of adipocyte lipolysis and its adrenergic control in trauma and sepsis has not been documented. It would appear that if endogenous substrate such as lipid is an important fuel during injury, then this system would play an important role. In this article we examine adipocyte lipolysis and its adrenergic control in patients with major trauma and sepsis.

Materials and Methods

Patients

Patients who were to have elective hip surgery were used as controls. Their adipose tissue biopsies were performed in the operating room after administration of general sodium pentathal anaesthesia but before the operation was started. Patients with trauma had multiple injuries requiring major surgery (Table 1). The adipose tissue biopsy specimens of these patients were taken in the surgical intensive care unit (SICU), within 24 hours after the patient had had surgery and with the patients not in shock. The patients with trauma had a second biopsy 4 days after their trauma. The patients with sepsis were those admitted to the SICU with a clinical diagnosis of sepsis (Table 1). Their adipose tissue biopsy specimens were taken 24 hours after the patients were admitted to the SICU, having had volume resuscitation and with the patients not in shock. The patients with sepsis also had biopsies performed after 4 days. None of these patients was receiving a major exogenous caloric source during the biopsies.

Biopsy

A biopsy was done of adipose tissue from the subcutaneous tissue of the anterior abdominal wall by a needle aspirate technique.[11] The tissue was transferred to a thermos containing 0.9 g/dL saline (37 C) and transported to the laboratory.

Preincubation

In the laboratory the tissue was dissected free from other fibrous tissue and cut into multiple small pieces. After rinsing with normal saline 0.9% at 37 C, the tissue was preincubated at 37 C for 30 minutes in 20 mL of preincubation media. The preincubation media contained a solution of 8 g/dL dialyzed bovine fatty acid–poor albumin mixed with an equal volume of double-strength Krebs-Henseleit original Ringer's bicarbonate buffer.[12] Glucose was added to give a final concentration of 4.16 mM. The adipose tissue was washed again over a nylon filter with warm 0.9 g/dL saline.

Incubation

Aliquots (20 mg) were placed in separate 15-mL polypropylene vials containing 2 mL of the isotopic incubation media and the various pharmacologic agents. To prepare the incubation media, labeled palmitic (9,10-^{3}H[N]) (NET-043, New England Nuclear, Boston, MA) of specific activity of 17 Ci/mmol was repurified in an aqueous ethanol heptane system. A thin film of approximately 6 Ci/mole was prepared by evaporation of twofold molar excess of ethanolic sodium hydroxide with labeled and unlabeled palmitic acid (Fischer Scientific). An 8 g/dL solution of dialyzed bovine fatty-poor albumin (Fraction V, Sigma Chemicals, St. Louis, MO) at pH 7.4 was added to the film to produce a final palmitate concentration of 1.0 mM. The molar ratio of fatty acid to albumin was approximately 1:1. The final incubation media (pH 7.4) was prepared by mixing equal volumes of the albumin–palmitate solution with double-strength Krebs-Henseleit original Ringer's bicarbonate buffer (gassed with 95% O_2 and 5% CO_2) and glucose to produce glucose, palmitate, and albumin concentrations of 4.16 mM, 0.5 mM, and 4 g/dL, respectively. Sufficient ^{14}C glucose D-(^{14}C[U])-glucose (NEC 042, New England Nuclear) in 0.9 g/dL saline was added to give a glucose-specific activity of approximately 2 Ci/mole. The addition of the labeled glucose increased the final glucose concentration in the media to 5–6 mM. The final media volume in each vial was 2.2 mL, and a gas phase was added to each vial containing 95% oxygen and 5% carbon dioxide. The tissue samples were incubated in triplicate in separate vials for each concentration of either isoproterenol, clonidine, or theophylline. After incubation for 2 hours at 37 C in a shaking bath, the tissue was separated from the incubation media over a nylon filter, washed with distilled water, and then placed in 5 mL of chloroform–methanol 2:1, v:v for extraction of lipids.

Pharmacologic Agents

To stimulate the beta-receptors, L-isoproterenol d-bitartrate salts (Sigma Chemicals) was used. To stimulate the alpha-2-receptors, clonidine hydrochloride (Sigma Chemicals) was used. These reagents were mixed on the day of the study with the use of 0.9 g/dL saline to produce concentrations from 1×10^{-4} to 1×10^{-8} M. Maximal stimulation of the hormone-sensitive lipase at a subreceptor level was achieved by use of theophylline (Sigma Chemicals) at a concentration of 3×10^{-4} M. The theophylline was mixed on the day of the study with the use of a solution of 0.45 g/dL fatty acid dialyzed bovine albumin. Theophylline (3×10^{-4} M) was also added to each concentration of clonidine in order to stimulate lipolysis, which allowed the alpha-2-inhibition of lipolysis to be more obvious.

Tissue Extraction and Chemical Analysis

After incubation, each sample was washed with saline and placed in 5 mL of chloroform–methanol 2:1 (v:v) solution layered with 10 mL of demineralized water at 5 C to extract the triglycerides. The solvent mixture was then layered with 10 mL of demineralized distilled water phase to generate a lower phase of chloroform containing the lipids. The water phase was changed in 24 hours and then removed after an additional 24 hours. The chloroform layer was transferred to small vials, where it was air dried to evaporate the chloroform, leaving the lipid. The samples were warmed on the final day of extraction and resuspended in 0.8 mL of chloroform. A 0.20-mL aliquot was then placed on a silica gel absorbent thin-layer chromatographic sheet (No. 13179 Eastman Kodak, Rochester, NY) and was run in a solvent of diethyl ether–hexane 1:9 (v:v) that clearly separates the triglycerides. The spot on the plate containing the triglycerides was cut out from the plate and placed in a scintillating vial with 10 mL of scintillating fluid (Aquasol, New England Nuclear, Boston, MA). The vials were then counted for ^{3}H and ^{14}C in a liquid scintillating beta counter (Beckman Instruments, Fullerton, CA) with quench correction.

Calculations

The media used for each experiment were counted in the scintillating counter to determine the exact specific activity of palmitate and glucose. The ratio of DPMs ^{14}C to DPMs ^{3}H was determined for the triglyceride spot of each tissue sample. When corrected for the specific activity of the ^{14}C-glucose and the ^{3}H-palmitic acid in the media, this ratio is designated the lipolysis factor. The lipolysis factor ratio is an index of lipolysis. When lipolysis is increased, the ratio is increased and *vise versa.*[12] The tissue stimulated with varying concentrations of isoproterenol (dissolved in 0.9 g/dL saline) provided a response curve for the beta-1-receptors. The tissue stimulated with the varying concentrations of clonidine (dissolved in 0.9 g/dL saline with theophylline) provided a response curve for the alpha-2-receptors. Each of the clonidine concentrations had theophylline added. This stimulated the adipocyte, allowing the inhibitory effect of the clonidine to be more obvious. The theophylline effect was then subtracted from the clonidine results to give a true clonidine effect, which results in a negative value because the clonidine is inhibitory.

The lipolysis factor at maximal beta-1 or alpha-2 stimulation is the responsiveness of the receptor, Vmax, a measure of the postreceptor response. The beta-1- and alpha-2-receptor data are then expressed as a percentage of the Vmax for each pharmacologic concentration to create a dose response curve for each receptor. These curves are then linearized by logit transformation.[13] The slope of the logit transformation of the dose response curve is related to receptor sensitivity. The receptor sensitivity is a reflection of both receptor number and agonist affinity.

Statistics

Triplicate determinations of the lipolysis factor for each pharmacologic effect of the individual tissue samples were averaged. This value was then used from each patient to calculate the mean response for the pharmocalogic effect of the group for normal patients and those with trauma and sepsis. The mean lipolysis factor for the basal, isoproterenol, and clonidine concentrations of the normal patients and those with trauma and sepsis were compared by an analysis of variance.[13] The theophylline values, and the Vmax, and slopes of the response curves of the samples were also compared by analysis of variance.

Results

The data for basal lipolysis are presented in Figure 1. The lipolysis factor for early trauma was 15.3 ± 1.3, which was significantly ($p < 0.05$) reduced 44.6% from the normal value of 27.6 ± 2.7. After 4 days the basal lipolysis factor for the patients with trauma was 19.3 ± 1.3, which was reduced from that of the normal patients but not significantly. In early sepsis the basal lipolysis factor was 55.0 ± 5.7, which was significantly increased ($p < 0.01$) over that of the normal patients by 99.3%. After 4 days the basal lipolysis factor for the patients with sepsis was 17.0 ± 2.9, which was decreased from the normal value of 27.6 ± 2.7 by 38.4%.

The data for the beta-adrenergic receptors for the three patient groups are presented in Table 2. In early trauma the beta-stimulated lipolysis factor is significantly ($p < 0.05$) decreased from the normal values (Fig. 2). After 4 days the curve has shifted toward normal and is not significantly different from the normal values. With early sepsis there was a significant ($p < 0.05$) increase in the beta-stimulated lipolysis factor as compared with normal values (Fig. 3). After 4 days the curve for the patients with sepsis had shifted below the normal curve. The lipolysis factors at isoproterenol concentrations of 1×10^{-5} M, 1×10^{-6} M, and 1×10^{-8} M were significantly ($p < 0.05$) less than those of the normal patients.

The beta-receptor Vmax (receptor responsiveness) for the patients with early trauma was 66.4 ± 3.8, which is statistically ($p < 0.05$) less 17.2% than the normal value of 80.2 ± 6.3 (Table 2) and significantly less 48.7% than the early sepsis value. After 4 days the beta Vmax for the group with trauma was 100.5 ± 9.7, which was not significantly different from the Vmax for the normal patients. With the patients with sepsis, the Vmax for the beta-receptors was 129.5 ± 12.8 in early sepsis, which is significantly ($p < 0.01$) elevated 61.5% above the Vmax of 80.2 ± 6.3 for normal patients (Table 2). After 4 days the beta-receptor Vmax for the patients with sepsis was 41.5 ± 5.2, which was significantly ($p < 0.01$) decreased 48.3% from the normal value.

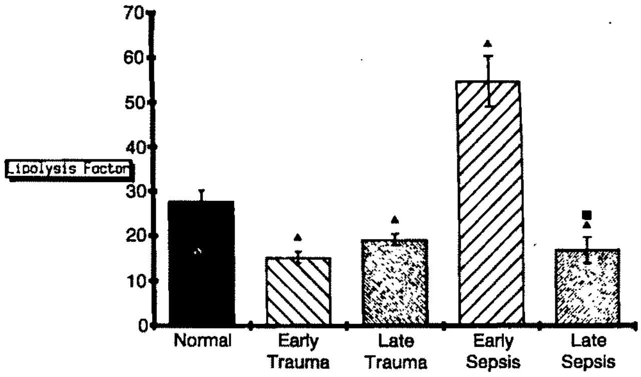

FIG. 1. Histogram of the basal lipolysis for all five groups, including the normal patients and those with early trauma, late trauma, early sepsis, and the late sepsis. The data presented are the lipolysis factors for each group. The ▲ indicates a significant difference ($p < 0.05$) from the normal values by an analysis of variance. The ■ indicates a significant ($p < 0.05$) difference of late from early by analysis of variance.

For the patients with early trauma, the slope of the response curve for the beta-receptors is 0.95 ± 0.03 (Table 2), which was significantly ($p < 0.05$) less than the normal slope of 1.09 ± 0.05. After 4 days the slope of the line was 1.02 ± 0.01, which was not statistically different from that for the normal patients. In early and late sepsis the slope was 1.23 ± 0.03 and 1.27 ± 0.06, respectively. Although both of these are decreased from the normal values, the differences were not significant.

The results for the alpha-receptors are presented in Table 3. In early trauma there was no difference in the decrease in the lipolysis factor with clonidine when compared with the decrease with the normal patients (Fig. 4). After 4 days the patients with late trauma had an increased alpha inhibitory effect as compared with normal patients. This was significant ($p < 0.05$) at a clonidine concentration of 1×10^{-5} M. With early sepsis there was an increase in the lipolysis factor with clonidine that was significant ($p < 0.05$) at concentrations of 1×10^{-7} and 1×10^{-5} (Fig. 5). These data support an inhibition of the alpha inhibitory effect in early sepsis. After 4 days the alpha inhibitory effect of the patients with sepsis was less than that of the normal patients, being significant ($p < 0.05$) at concentrations of 1×10^{-5}

TABLE 2. *Beta-adrenergic Receptor Data for Normal Patients and Both Groups of Patients with Sepsis and Trauma*

	Normal	Early Sepsis	Late Sepsis	Early Trauma	Late Trauma
Sample number	10	10	5	5	3
Isoproterenol 1×10^{-5}	72.1 ± 6.5	126.4 ± 12.1*	40.9 ± 5.3*†	67.4 ± 3.6	100.4 ± 9.7†
Isoproterenol 1×10^{-6}	60.2 ± 4.7	107.3 ± 9.9*	35.7 ± 4.6*†	36.0 ± 3.9*	80.5 ± 12.6†
Isoproterenol 1×10^{-7}	38.9 ± 3.9	71.2 ± 5.6*	26.8 ± 5.0†	16.3 ± 1.0*	27.8 ± 3.3
Isoproterenol 1×10^{-8}	29.7 ± 6.3	54.9 ± 2.9*	23.2 ± 5.2*†	15.3 ± 1.1*	21.5 ± 1.5
Vmax (responsiveness)	80.2 ± 6.3	129.5 ± 12.8*	41.5 ± 5.2*†	66.4 ± 3.8	100.5 ± 9.7†
Slope of the response curve (sensitivity)	1.09 ± 0.05	1.23 ± 0.04*	1.28 ± 0.05*	0.95 ± 0.03*	1.02 ± 0.01

* Significantly different ($p < 0.05$) from normal by analysis of variance.

† Late significantly different ($p < 0.05$) from early by analysis of variance.

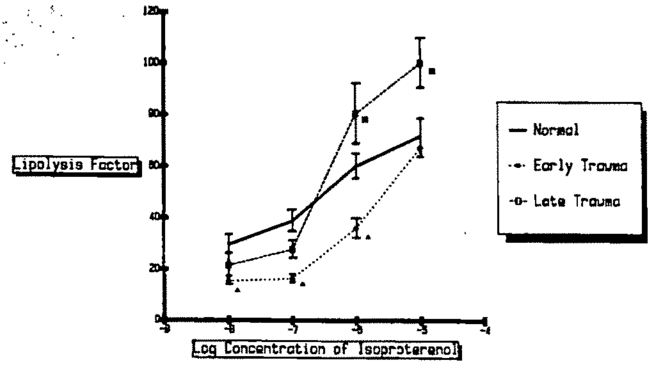

FIG. 2. Data for the beta-receptors. The lipolysis factor is plotted against the log concentration of the beta-agonist isoproterenol. The data are for the normal patients as well as for those with early and late trauma. The ▲ indicates a significant difference ($p < 0.05$) from the normal values by an analysis of variance. The ■ indicates a significant ($p < 0.05$) difference of late from early by analysis of variance.

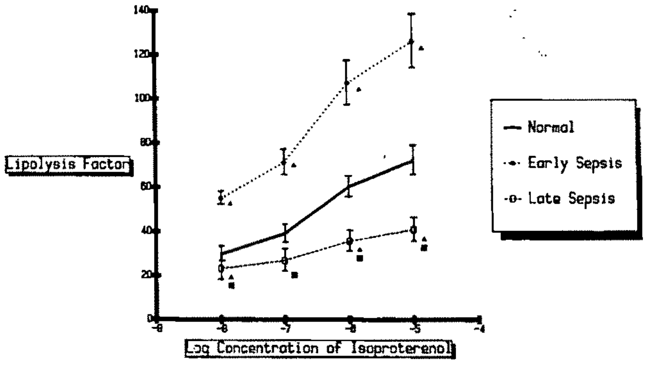

FIG. 3. Data for the beta-receptors. The lipolysis factor is plotted against the log concentration of the beta-agonist isoproterenol. The data are for the normal patients as well as for those with early and late sepsis. The ▲ indicates a significant difference ($p < 0.05$) from the normal values by an analysis of variance. The ■ indicates a significant ($p < 0.05$) difference of late from early by analysis of variance.

and 1×10^{-6} M. This indicates a increased alpha effect with late sepsis.

The maximal alpha effect or alpha responsiveness was achieved with a clonidine concentration of 1×10^{-5} M. In the patients with trauma the alpha Vmax for early trauma was −27.5 ± 7.4, which was similar to the −31.2 ± 3.2 for the normal patients (Table 3). In the group with late trauma the alpha Vmax had increased to −54.0 ± 7.2, which was significantly ($p < 0.05$) greater than the normal alpha Vmax. Patients with early sepsis had an alpha Vmax of −45.1 ± 7.2, which was significantly ($p < 0.05$) greater then the normal value. After 4 days their Vmax had decreased to a value of −19.9 ± 4.3, which was a significant ($p < 0.05$) decrease as compared with the normal Vmax and the Vmax of the group with early sepsis.

With both early and late trauma, the slopes of the response curve for the alpha-receptors were 0.82 + 0.02 and 0.80 + 0.11, respectively, and were not significantly different from the normal slope of 0.73 + 0.04 (Table 3). With early sepsis the slope of the alpha response curve was not significantly different from that of the normal patients. After 4 days the slope for the patients with sepsis was 0.78 + 0.11, similar to that of the normal patients.

The subreceptor stimulation was carried out by use of theophylline. These data are presented in Table 3. The theophylline-stimulated lipolysis factor for the patients with early and late trauma were not significantly different than the normal value. Those patients who had early sepsis had a theophylline-stimulated lipolysis factor of 110.4 + 10.7, which was significantly ($p < 0.01$) greater than the normal value. In late sepsis the theophylline stimulation resulted in a lipolysis factor of 35.4 + 5.8, which was less than that of the normal patients and significantly ($p < 0.05$) less than the early sepsis value.

Discussion

There are differences in fat metabolism between patients with normal trauma and those with sepsis. These data have principally come from studies on muscle metabolism, liver metabolism, and the alterations in the serum levels of FFAs, triglycerides, and lipoproteins.[4–6] The results of this study again indicate that there are major differences in fat metabolism between trauma

TABLE 3. *Data for Theophylline Stimulation and the Alpha-Adrenergic Receptors for the Normal Patients and both Groups of Patients with Trauma and Sepsis*

	Normal	Early Sepsis	Late Sepsis	Early Trauma	Late Trauma
Sample number	10	10	5	5	3
Theophylline	52.9 ± 3.8	110.4 ± 10.7*	35.7 ± 5.8†	48.4 ± 10.0	79.0 ± 10.7
Clonidine 1×10^{-5}	−28.0 ± 3.8	−39.1 ± 7.6*	−19.0 ± 4.5*†	−22.1 ± 6.8	−53.2 ± 11.2*†
Clonidine 1×10^{-6}	−27.3 ± 3.5	−30.9 ± 7.3	−18.7 ± 3.7*†	−21.6 ± 6.9	−52.9 ± 12.4*†
Clonidine 1×10^{-7}	−21.1 ± 3.4	−23.3 ± 6.6	−13.9 ± 4.7†	−15.9 ± 4.0	−36.7 ± 9.4
Clonidine 1×10^{-8}	−10.8 ± 1.2	−8.7 ± 5.6	−7.1 ± 2.8	−5.5 ± 1.6	−15.3 ± 8.0
Vmas (responsiveness)	−31.2 ± 3.2	−45.1 ± 7.2*	−19.9 ± 4.3*†	−27.5 ± 7.4	−54.0 ± 7.2*†
Slope of the response curve (sensitivity)	0.73 ± 0.04	0.77 ± 0.05	0.78 ± 0.11	0.82 ± 0.02	0.80 ± 0.11

* Significantly different ($p < 0.05$) from normal by analysis of variance.

† Late significantly different ($p < 0.05$) from early by analysis of variance.

and sepsis. In early trauma there is a decrease in *in vitro* basal lipolysis, beta stimulation of lipolysis, and beta-receptor responsiveness. These findings are explained by an increased beta-adrenergic stimulation *in vivo* and stimulation of lipolysis. The decreased beta stimulation of the adipocytes of patients with trauma is the well-described phenomenon of desensitization. The term desensitization is used to describe a state of diminished hormonal response that follows after exposure to catecholamines.[15,16] This state has been previously reproduced with the adrenergic receptors of human adipocytes. The results of that study indicated that the desensitization from catecholamine exposure occurred with the beta-receptors but not with the alpha-receptors.[16] The results of our study are in complete agreement with these previous findings. A similar situation has been described in patients with pheochromocytoma where there is resistance of the adipose tissue to stimulation by catecholamines *in vitro*.[14,16] One of the most common mechanisms for desensitization is a decrease in receptor number, which is referred to as "down regulation."[14,15,17] Our data suggest that desensitization in early trauma results in part from down regulation of the beta-receptor as there was a significant decrease in the receptor sensitivity or number. Again, desensitization with down regulation is most commonly caused by prolonged exposure of the receptor to catecholamines. Another possible mechanism for beta-receptor desensitization with down regulation is alteration in the receptor affinity. This theory has received support from recent studies demonstrating that there is phosphorylation of the beta-receptor after prolonged catecholamine exposure, resulting in alteration of the receptor affinity.[14,19]

The receptor data from patients with trauma are consistent with down regulation as a result of the 24-hour catecholamine exposure before the biopsy. Our data further support the relationship of the beta-receptor desensitization and down regulation to catecholamine exposure in that after 4 days the adipocytes of the patients with trauma were similar to those of the normal patients. The plasma level of catecholamines has returned to normal by the 4th day after major surgery,[18] a stress similar in magnitude to that of our patients with trauma.

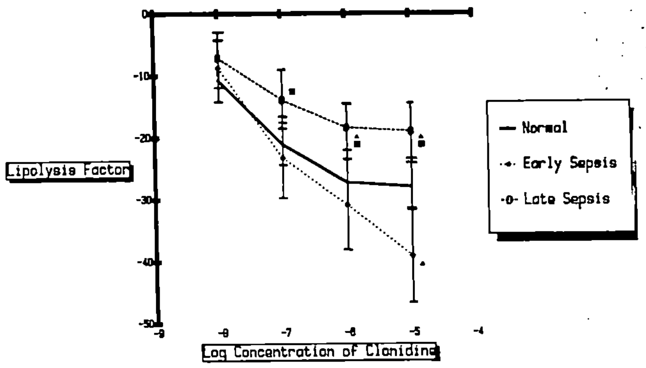

FIG. 4. Data for the alpha-receptors. The lipolysis factor is plotted against the log concentration of the alpha-agonist clonidine. The lipolysis factor is recorded in the negative as the alpha-receptor decreases lipolysis. The data are for the normal patients as well as for the patients with early and late trauma. The ▲ indicates a significant difference ($p < 0.05$) from the normal values by an analysis of variance. The ■ indicates a significant ($p < 0.05$) difference of late from early by analysis of variance.

The alpha-receptor data in the traumatized patient are interesting. With early trauma there is essentially no change from the normal alpha-receptors; however, after 4 days the alpha-receptors have an increased activity with increased responsiveness. These alpha-receptor findings in late trauma are similar to those of alpha-receptors that have not been stimulated, such as with denervation hypersensitivity. In these situations there is an greater response after time. This has been demonstrated in studies of the heart, where, when the catecholamine level has been decreased for a prolonged time, there was a greater response to subsequent catecholamine exposure.[20,21] These previous studies suggested that this hypersensitivity resulted from an increase in the number of receptors, or "up regulation" of the receptors. The alpha-receptor data in the patients with trauma had alpha-hypersensitization but without up regulation. It would appear that there was a period of time in which the alpha-receptors were not stimulated, which accounts for this receptor hypersensitivity. At present there are insufficient data on the alpha-receptors, and particularly with the human adipocyte, to completely explain this phenomenon.

In general, the adipocyte of the patient with trauma supports other data indicating increased adrenergic-stimulated lipolysis during early injury (Table 4). After 4

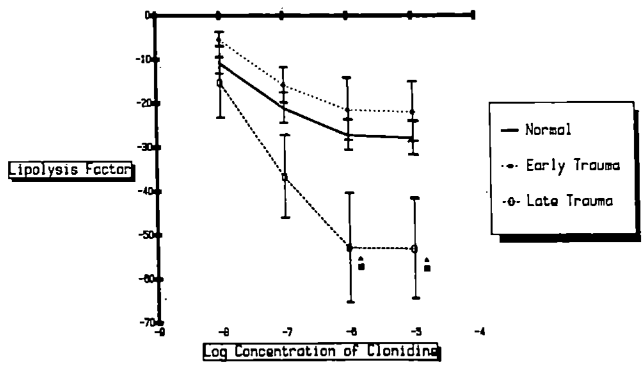

FIG. 5. Data for the alpha-receptors. The lipolysis factor is plotted against the log concentration of the alpha-agonist clonidine. The lipolysis factor is recorded in the negative as the alpha receptor decreases lipolysis. The data are for the normal patients as well as for the patients with early and late sepsis. The ▲ indicates a significant difference ($p < 0.05$) from the normal values by an analysis of variance. The ■ indicates a significant ($p < 0.05$) difference of late from early by analysis of variance.

TABLE 4. *Summary of Receptor Results*

Patients	Beta-receptor State *In Vitro*	Interpretation *In vivo*	Effect on Lipolysis	Alpha-receptor State *In Vitro*	Interpretation *In Vivo*	Effect on Lipolysis
Early trauma	Desensitization with down regulation	Increased stimulation	Increased lipolysis	No change	Normal situation	No change
Late trauma	Normal response	Normal situation	No change	Hypersensitization	Decreased stimulation	Increased lipolysis
Early sepsis	Hypersensitization with up regulation	Decreased stimulation (inhibited)	Decreased lipolysis	Hypersensitization	Decreased stimulation (inhibited)	Increased lipolysis
Late sepsis	Desensitization with up regulation	Increased stimulation	Increased lipolysis	Desensitization	Increased stimulation	Decreased lipolysis

days the adipocyte data indicate a reduction in the lipolysis that corresponds to the turning point of these patients toward the convalescence period.

In the patients with sepsis the adipocytes react very differently. With early sepsis there was an increase in basal lipolysis, beta stimulation, beta responsiveness, and beta sensitivity. These data indicate that the beta-receptors have developed hypersensitivity. This finding would suggest that the beta-adrenergic receptor was not stimulated *in vivo.* However, the catecholamine levels are very elevated with sepsis,[22] and remain elevated for a long time as a result of the prolonged stress state.[22,23] Thus, it would appear that the beta-receptors were not affected by the elevated catecholamine levels. The beta-receptor hypersensitivity in early sepsis is associated with up regulation of the receptors. This is similar to the denervation hypersensitivity in which there is an increase in receptor number because of the lack of stimulation. Beta-receptor hypersensitivity has been seen in other beta-receptor systems.[19,24,25] In these studies there was uncoupling of the receptor mechanism from the adenylate cyclase involved with the post–receptor stimulation and alterations in the protein structure.[19,20] The data from this study suggest that in early sepsis there is a block of the beta-adrenergic receptors of the adipocyte. This would most likely result from one of the circulating factors in sepsis. It is interesting to note that *Escherichia coli* endotoxin has been shown to block the effect of catecholamine stimulation of beta-receptors on animal adipocytes.[26]

In late sepsis, basal lipolysis and beta-receptor stimulations are decreased after 4 days, with a significant decrease in receptor responsiveness. This is similar to results of early trauma representing desensitization of the beta-receptors and adrenergic stimulation of lipolysis. As with trauma, this most likely results from the effect of the catecholamine levels that are still elevated in these patients. Unlike in the trauma situation, the beta-receptors of late sepsis do not have a decrease in the receptor sensitivity or receptor number. It is possible that, with the initial hypersensitivity of the beta-receptor, the subsequent stimulation does not result in the decrease or down-regulation of the receptor.

In the adipocytes from the patients with early sepsis there was an increase in the alpha-receptor response and the postreceptor mechanism with no change in the alpha receptor number. This again represents receptor hypersensitivity without up regulation of the receptors. Thus, as with the beta-receptors in early sepsis, there appears to be an *in vivo* block or inhibition of the alpha-receptor complex. The block prevents the alpha-receptors from being affected by the high circulating levels of catecholamines in early sepsis. It is possible that this alteration of the alpha-receptors is similar or coupled to that of the beta-receptors. These alterations of the alpha-receptors in early sepsis will need further study, and there is no current evidence that endotoxin alters these receptors. It is possible that other circulating factors are involved with these adrenergic alterations in early sepsis.

The alpha-receptor response was decreased in late sepsis with a decreased alpha responsiveness. This pattern is similar to one described with adipose tissue from patients with hyperthyroidism and increased catecholamine stimulation of the alpha-receptors. In that situation the alpha-receptors were desensitized with both down regulation and altered responsiveness.[18] Our data demonstrate the altered responsiveness but do not show the decrease in receptor number. At present, because of the limited research done on the alpha-receptors, we are unable to explain the significant alteration in the alpha-receptor number or affinity.

The alterations in the adrenergic receptors and basal lipolysis reported here would suggest that there was a decrease in adipocyte adrenergic-stimulated lipolysis in early sepsis. The data suggest that it results from a reversible block of the adrenergic system (Table 4). After 4 days both the beta- and alpha-receptors are altered again but this time indicate an increased adrenergic effect and increased lipolysis. The object to understanding these early receptor alterations in sepsis would be to determine if these alterations result in a significant decrease in lipolysis and thus the availability of endogenous lipid for fuel. If this were the case it could explain in part the increased protein catabolism in patients with sepsis.

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Aminoterminal Propeptide of Type III Procollagen in Healing Wound in Humans

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For quantitative analysis of wound healing in surgical patients, samples of wound fluid were collected through a silicone rubber tube and their concentration of the aminoterminal propeptide of type III procollagen was measured with a specific radioimmunoassay. Peritoneal fluid, collected through an abdominal drain, and serum were also analyzed. At day 1 after operation, the mean concentration of the propeptide was 30 times higher than the mean preoperative serum level (2.5 μg/L). A significant increase ($p < 0.001$) occurred at day 3 in the wound and at day 2 in peritoneal fluid. At day 5 the mean wound concentration (2670 μg/L) was 1000 times higher than the serum level. In serum a small but significant increase ($p < 0.05$) was found at days 5 and 30. The increase in wound fluid resulted from the intact, liberated propeptide, indicating that the results reflect the synthesis of type III collagen deposited in the wound. This procedure offers a quantitative tool for wound healing studies. Other extracellular matrix components can also be measured, the sequential pattern of their appearance can thus be assessed, and disturbances and treatment effects in wound healing can be detected.

EARLY STRENGTH of a healing wound is mainly based on a load-resistant myofibroblast–reticulin network that connects the wound margins. The exact biochemical nature of this reticulin is not known, but it is thought to consist of fibronectin, type III collagen, and other compounds.[1] Later this network is replaced by more dense connective tissue, which contains increasing amounts of type I collagen. Immunohistochemical studies have shown that type III procollagen and collagen appear in granulation tissue 1 day after wounding, but the first signs of type I collagen are seen 2 days later.[2,3]

The fiber-forming collagens (types I–III) are synthesized as procollagens, which contain additional propeptide extensions at both ends. These are cleaved off *en bloc* when collagen molecules are deposited into the tissue. The complete removal of the carboxyterminal propeptides is necessary for fiber formation, whereas not all the aminoterminal propeptides, especially those of type III collagen, are cleaved. Such pN type III collagen molecules are found on the surface of the fibers, where they most likely prevent further growth of the fibril.[4] The liberated propeptides can be found and their concentration measured in the extracellular fluid and in circulation. The assay for the aminoterminal propeptide of type III procollagen in serum has been used in a number of clinical studies.[5,6] However, the antigens detected in serum are heterogenous, because the degradation of tissue pN type III collagen and further degradation of the propeptide itself form larger and smaller antigens than the propeptide, respectively.[7]

We have recently developed a modification of the assay for the aminoterminal propeptide of type III procollagen based on the purified human peptide.[8] The assay is not sensitive for the smaller degradation products. Here, for the first time, we demonstrate the quantitative analysis of this propeptide in wound and peritoneal fluid after abdominal surgery and compare the observed changes with those found in serum. In addition, the antigen heterogeneity is studied in wound fluid during the first 5 days of healing.

Materials and Methods

Patients

The cases of 18 consecutive, otherwise healthy, nonobese patients, 13 men and five women, were investigated (mean age: 45 years; range: 30–69 years). They

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were electively operated on at Oulu University Central Hospital for duodenal ulcer (proximal gastric vagotomy, seven patients); reflux esophagitis (Nissen fundoplication, six); gallstones (cholecystectomy, two); or for two of these reasons (three). For wound infection prophylaxis, a single dose of cefuroxime (1.5 g) was given intravenously at induction of anesthesia. Informed consent was obtained from each patient for participation in the study. The study was approved of by the Ethical Committee of the Medical Faculty of the University of Oulu.

Collection of Samples

For collecting wound fluid, two 15 cm Silastic silicone rubber tubings (Dow Corning medical grade tubing no. 602-235, external diameter 2 mm) were left subcutaneously for 120 hours at the end of the operation. The outer ends, closed with a clip, were conducted through separate stab skin incisions and secured with adhesive strips. After the tubings and the adjacent skin were cleansed with chlorhexidin solution (5 mg/mL), the daily samples of wound fluid were drawn into a 1.0-mL syringe by puncture of the tubing with a 18-G needle. A new clip was then applied proximal to the puncture site. The volume of the fluid was measured and the appearance determined visually as bloody, semiserous, or serous. As reported previously by Viljanto et al.,[9] no wound healing complications were associated with the presence of the tubings. The wound fluid samples of a female patient in whom a wound hematoma developed were excluded from the final results because the propeptide concentrations were low, approaching the serum levels. A few other samples are missing for technical reasons or were unintentionally not taken. Thus, the total numbers of wound fluid samples studied were 12, 12, 16, 13, and 13 for days 1–5, respectively.

Peritoneal fluid was obtained by puncturing the abdominal drain (Exudrain no. 18, Astra Meditec, Mölndal, Sweden) near the skin level and the appearance determined as above. The numbers of peritoneal fluid samples analyzed were 12, 11, and 8 for days 1–3, respectively. At day 3 the drains were removed, and at that time four of them were already dry. Serum samples were taken after overnight fasting from the patients before operation and 5 and 30 days after operation.

All the samples were stored at −20 C until analyzed. The wound and peritoneal fluid samples were initially diluted 1:10 with phosphate-buffered saline containing 0.04% of Tween 20 (ICI Americas, Wilmington, DE). All further dilutions were also made in this buffer.

Radioimmunoassays

A modification[8] of the assay for the aminoterminal propeptide of human type III procollagen was used that detects only the serum antigens that are similar in size to the intact propeptide or larger.[7,8] The antiserum and the assay conditions have been selected in order to diminish the interference caused by the small molecular weight degradation products of the propeptide (see Fig. 1). Thus, the standard antigen and samples of biologic fluids give parallel inhibition curves. Briefly, 0.1 mL of an antiserum dilution (rabbit no. 70) capable of binding 50% of the labeled antigen was incubated for 2 hours at +37 C with 0.2 mL of nonlabeled standard antigen or unknown sample before addition of the I^{125}-labeled human aminopropeptide. After 1 hour of incubation at +37 C, the free and bound antigens were separated by precipitation (overnight at +4 C) with goat antiserum against rabbit IgG. The precipitate was isolated by centrifugation for 30 minutes at +4 C and washed once, and the radioactivity was counted with a Multigamma gamma counter (LKB–Wolloc, Turku, Finland). An assay was also used to analyze the antigenic profile of wound fluid that detects both the propeptide and its degradation products (see below).

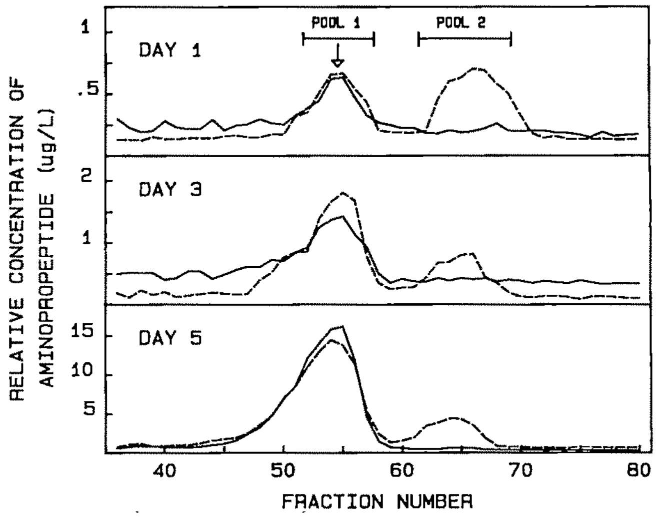

FIG. 1. Sephacryl S-300 gel filtration analysis of the profile of antigens related to the aminoterminal propeptide of type III procollagen in wound fluid. Two different radioimmunoassays were used (for details see "Materials and Methods"): one that measures only the intact propeptide (solid line) and another that detects both the propeptide and its degradation products (dashed line). Two pools were thereafter collected: pool 1 contained the propeptide, and pool 2 contained its degradation products. The exact amounts of the antigens in the pools (see Table 1) were then analyzed as described in "Materials and Methods." The arrow indicates an elution position of the isolated aminoterminal propeptide of human type III procollagen.[15] Note the different scales of the propeptide concentrations at days 1, 3, and 5.

For each wound or peritoneal fluid sample, a dilution curve containing three to five points was made. The results were calculated with the 50% intercept method.[6] This was obtained with a Kaypro 16 microcomputer (IBM compatible) (Kaypro Co., Solana Beach, CA) using a program[10] in which logit and log transformations

TABLE 1. *The Content of the Aminoterminal Propeptide of Type III Procollagen and its Degradation Products in Wound Fluid at Days 1, 3, and 5 in the Same Patient*

	Concentration*		Pool 1†		Pool 2†	
Day	μg/L	-Fold	ng	-Fold	ng	-Fold
1	124	1.0	10.5	1.0	9.0	1.0
3	407	3.3	31.2	3.0	14.0	1.6
5	2777	22.4	237.0	22.6	44.6	5.0

* Propeptide concentration in wound fluid as measured with the standard radioimmunoassay (antiserum no. 70) before gel filtration.

† The pools are indicated in the gel filtration profile (Fig. 1). The amounts of the intact propeptide (pool 1) and its degradation products (pool 2) were analyzed as described in "Materials and Methods."

are used to obtain a linear dose–response curve, followed by iterated weighted-least-squares regression analysis. In addition to the 50% intercept, the program calculates the slope of the inhibition curve for each sample: these were similar to that of the standard. The intra-assay variation was 7%.

Antigenic Profile of Wound Fluid

Wound fluid samples of 0.1 mL from days 1, 3, and 5, obtained from the same patient, were chromatographed on a column (1.5 × 110 cm) of Sephacryl S-300 (Pharmacia, Uppsala, Sweden) equilibrated in phosphate-buffered saline, pH 7.2, containing 0.04% Tween 20. Fractions of 2.5 mL were collected. Each fraction was then directly analyzed both with the radioimmunoassay described above and with an assay (using the antiserum from the rabbit no. 47) that detects both the propeptide and its degradation products, the latter with a less steep slope of the inhibition curve, however.[6] In molar terms, the same amounts of a major degradation product (the so-called Col1 domain), obtained after bacterial collagenase digestion, and of the intact propeptide were needed to obtain a 50% inhibition. After localizing the propeptide and its degradation products with the latter assay, two pools based on the inhibition profile were made (Fig. 1), pool 1 containing the propeptide and pool 2 its degradation products. The concentrations of the respective antigens were then estimated in the pools with the radioimmunoassay with antiserum no. 47, with the use of the intact propeptide or its Col1 domain as a standard antigen to eliminate the effect of different slopes of the inhibition curves (Table 1).

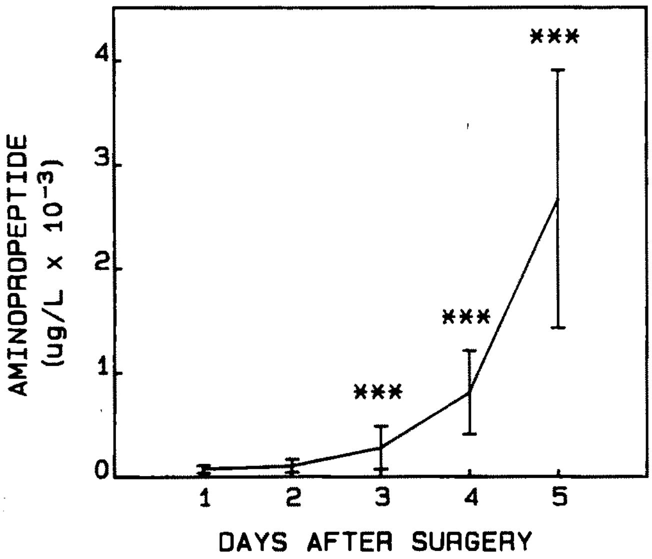

FIG. 2. Effect of time on the concentration of the aminoterminal propeptide of type III procollagen in wound fluid (mean ± SD). ***$p < 0.001$ compared with the concentration at day 1.

Statistical Analysis

Before comparing the propeptide concentrations in wound and peritoneal fluid at different time points, a logarithmic transformation was necessary because the variances differed (Bartlett's test), being dependent on the mean of the group. A one-way analysis of variance for repeated measurements was then performed and the significance of the differences in the concentration of propeptide, compared with the first day level, was tested using a modified t-test and calculating the critical t-value by the Bonferroni method.[11] The correlations between the wound fluid propeptide concentration and the other parameters were analyzed by use of the Pearson correlation coefficient or, for discrete measurements, the Spearman rank correlation coefficient.

Results

Aminopropeptide in Wound Fluid, Peritoneal Fluid, and Serum

The concentration of the aminoterminal propeptide of type III procollagen in wound fluid at day 1 was 75 ± 37 μg/L. It remained almost unchanged during the first 2 days after operation and increased rapidly thereafter (Fig. 2). On day 5 the mean concentration was 35-fold that of day 1. Compared with the mean preoperative serum level (see below), this indicates a 1000-fold concentration. A significant increase in propeptide concentration already occurred in peritoneal fluid (Fig. 3) between days 1 and 2 ($p < 0.001$). However, in the wound (Fig. 1) a significant change was evident only 3 days after surgery ($p < 0.001$).

In serum the propeptide concentration was significantly increased at day 5 ($p < 0.05$) and at day 30 ($p < 0.05$), compared with the preoperative values (Fig. 4). However, these concentrations were all within the reference interval, determined for healthy adults (1.7–4.2 μg/L).

Antigenic Profile of Wound Fluid

The radioimmunoassay applied for the fluid concentration analyses only detected one propeptide antigen species in wound fluid; this was of similar size as the propeptide, when cleaved off *en bloc* during the extracellular processing of type III procollagen (Fig. 1, solid line). The gel filtration profile indicates that no procollagen or other high-molecular-weight propeptide antigens are present in wound fluid. Thus, the cleavage of the aminoterminal propeptide, which often is not complete, has occurred efficiently during wound healing. Degradation products of the propeptide were detected by another radioimmunoassay (Fig. 1, dashed line). Because this assay also recognized the intact propeptide, the two antigen forms could be pooled separately (Fig. 1). The analysis of both pools with the use of proper standard antigens indicated that the concentration of intact propeptide had increased 22-fold by day 5, compared with day 1, and that of the degradation products only fivefold (Table 1).

Correlation Analysis

About one-third of the wound fluid samples were bloody at days 1 and 2. Later, at days 3–5, less than 10% contained visible blood. No correlation was found between the appearance of wound fluid and the aminopropeptide concentration. The mean volumes of fluid obtained on the five postoperative days were 215 μL (range: 70–600 μL); 200 μL (range: 90–500 μL); 180 μL (range: 70–430 μL); 145 μL (range: 70–240 μL); and 175 μL (range: 40–400 μL). There was no correlation between the volume and the propeptide concentration. The thickness of subcutaneous tissue also had no effect on the propeptide concentration in wound fluid.

Discussion

A lot of experimental data are available concerning wound healing, but human studies are hampered by technical and ethical difficulties in collecting samples of granulation tissue. However, two acceptable methods have been developed: the Cellstic[12] and a method using a miniature PTFE tube.[13] The former has been used for studying the appearance of cells,[14] collagen types,[3] and fibronectin[9] during early wound healing. The latter was used for histologic and hydroxyproline analyses.[13] In this study the silicone rubber tubing of the Cellstic device without viscose cellulose sponge was left subcutaneously in the wound, offering a gate for repeated wound fluid collection for at least 5 days after operation, and then a new method for analyzing the aminoterminal propeptide of type III procollagen was applied.[8] If such a quantitative analysis reflects the tissue events, then the problems encountered with tissue sampling are avoided.

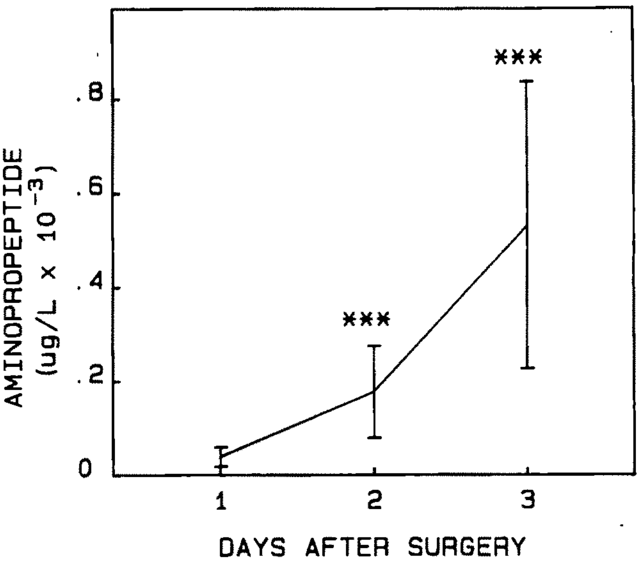

FIG. 3. Effect of time on the concentration of the aminoterminal propeptide of type III procollagen in peritoneal fluid (mean ± SD). ***p < 0.001 compared with the concentration at day 1.

The content of free aminoterminal propeptide of type III procollagen in wound fluid increased significantly 3 days after operation and continued to do so until day 5, which was the last day studied. This finding is in agreement with the previous immunofluorescence studies that demonstrated the first signs of type III procollagen and collagen 1–2 days after wounding and increasing amounts thereafter.[3] The concentration of the propeptide at day 5 was 1000-fold, compared with the normal serum level. At the same time there was a significant

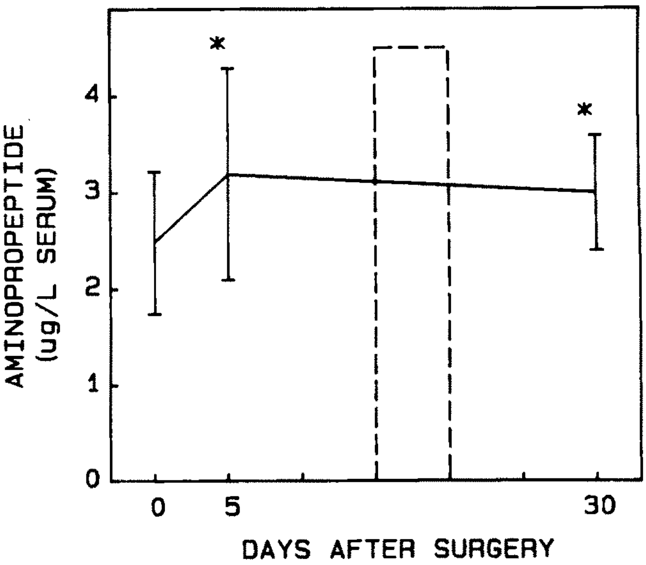

FIG. 4. Effect of abdominal surgery on the concentration of the aminoterminal propeptide of type III procollagen in serum (mean ± SD). The column indicates the reference range for nonoperated controls. *p < 0.05 compared with the preoperative level.

increase in the serum concentration, although the values remained within the reference range. Thus, the increase in the synthesis of type III collagen in the granulation tissue after moderate surgical trauma was large enough to be reflected in the serum.

The analysis of the antigenic profile in wound fluid indicated that the processing of type III procollagen was complete; only the liberated aminoterminal propeptide and no higher molecular weight forms were present in this extracellular fluid. The further degradation of the propeptide in the wound was also studied (Fig. 1). The increase in the concentration of the degradation products was smaller than that in the concentration of the intact propeptide (Table 1). Because most of the serum antigenicity results from the smaller fragments, however, the findings suggest that the evident further degradation does not take place *in situ,* but during the later stages of the propeptide elimination. The analysis of the gel filtration fractions with the new assay modification verified the fact that the degradation products of the propeptide are not interfering in this assay. The increased concentrations found in the wound result from increased amounts of the intact propeptide cleaved *en bloc* and not from the other antigen forms that predominate in serum.[7] Thus, the results seem to reflect the synthesis of type III collagen, which is also deposited in the wound granulation tissue.

The procedure described offers a new method of quantitative study of early events in human wound healing. Applying new immunoassays for different collagen types and other extracellular matrix components[5,6] will provide accurate information on the sequential pattern of their appearance and provide the possibility for detecting disturbances in the healing process itself. Also, the effects of different treatment regimens could be compared easily.

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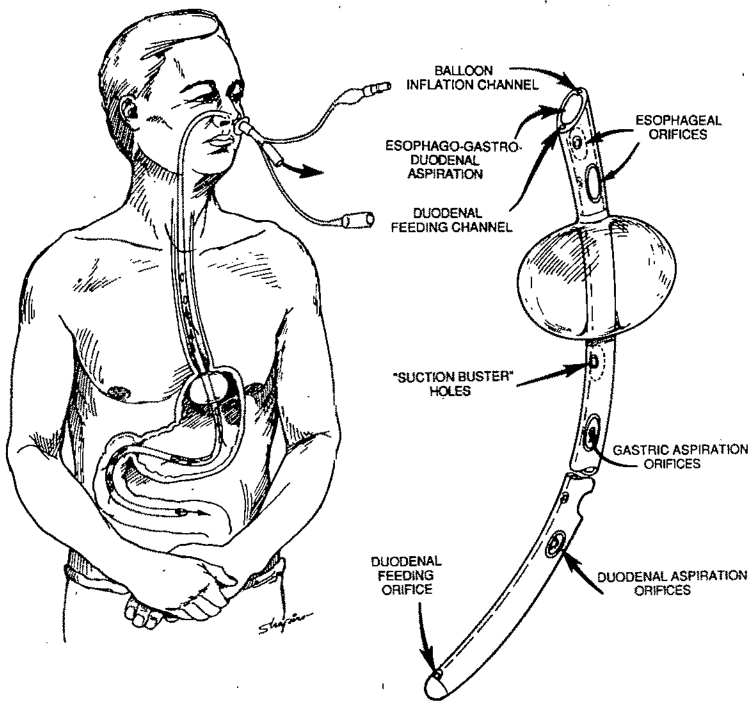
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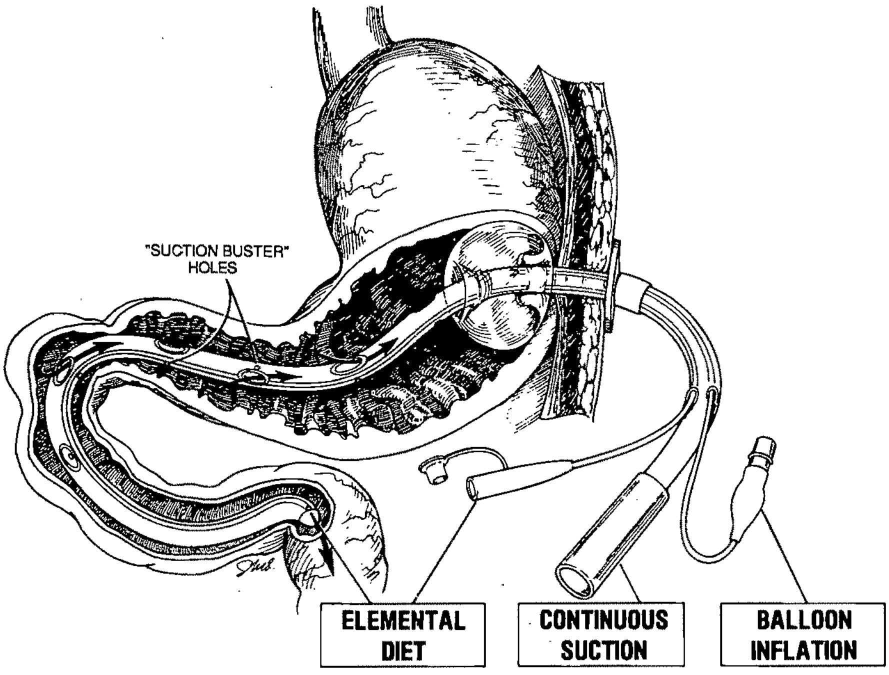

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CASE # 24 **AGE:** 55 **SEX:** FEMALE

DIAGNOSIS: CECAL CARCINOMA

SYMPTOMS: ANEMIA (Hg 6 gm/dl)

OPERATION: RIGHT HEMICOLECTOMY & GASTROSTOMY

The patient had a right hemicolectomy with stapled (U.S. Surgical Corp) anastomosis and fascia closure and a MOSS® gastrostomy tube. The stomach and proximal duodenum were aspirated, with immediate simultaneous feeding into the distal duodenum.

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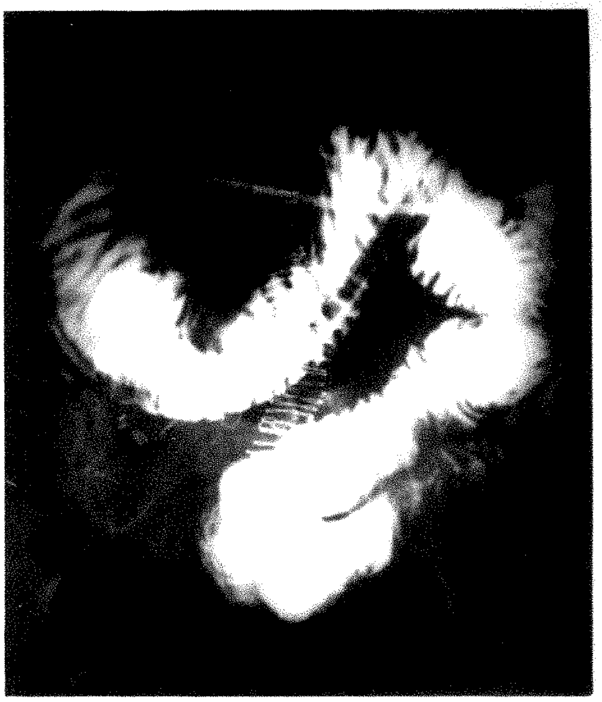
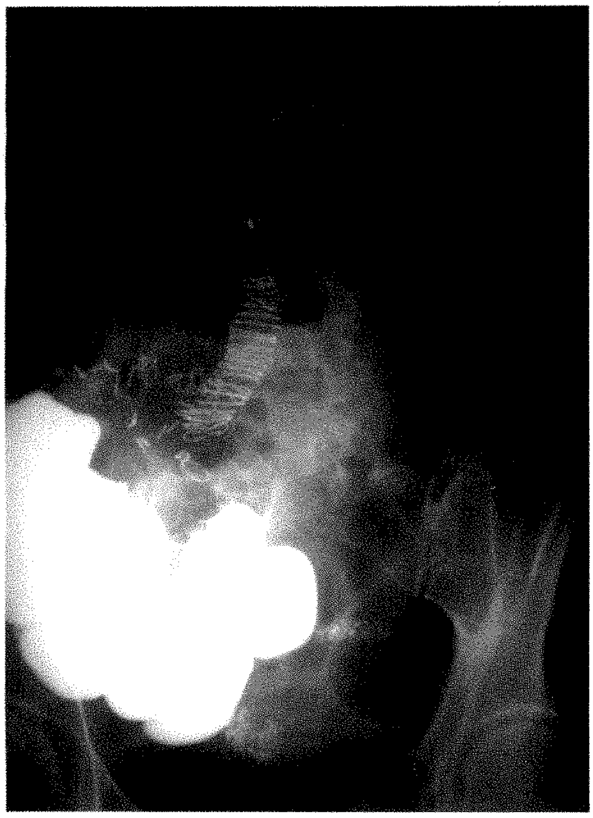
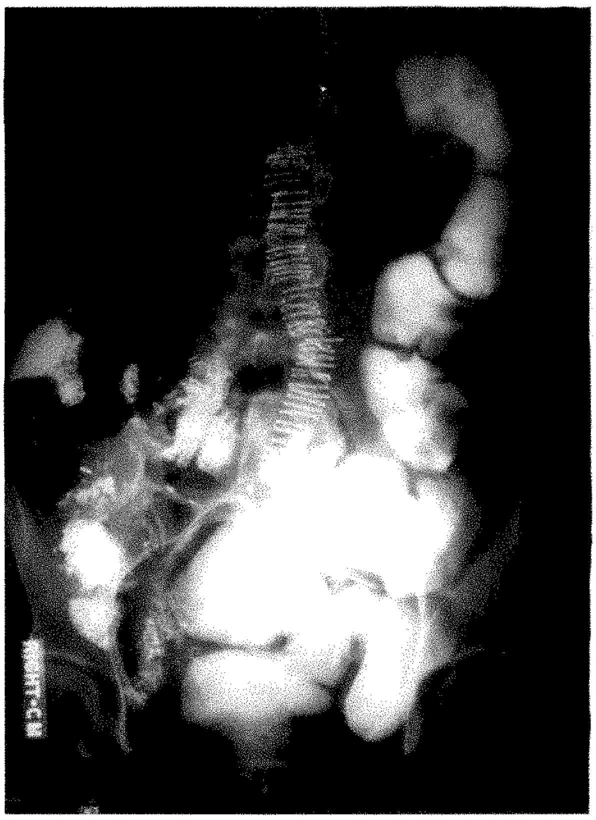
She received 300 ml/hr of Vivonex TEN (Norwich Eaton Pharm), absorbed 5,000 kcal the initial 20 hours, and then tolerated a general diet. She was the 4th patient discharged uneventfully 24 hours after bowel resection and reanastomosis.



A. Study @ 5 minutes (5 hours postop).
Note efficient removal of all excess barium, with none reaching the stomach.



B. Motility @ 4 hours (9 hours postop).
All barium is within the ileum.



C. Motility @ 16 hours (21 hours postop).
Barium is exiting in a spontaneous bowel movement.

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Continued from page 33A

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Inhibition of Vessel Allograft Rejection by Endothelial Removal

Morphologic and Ultrastructural Changes

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From the Orthopaedic Research Laboratories, Department of Pathology,† and Department of General and Thoracic Surgery,‡ Duke University Medical Center, Durham, North Carolina*

The vascular endothelium plays an important and complex role in vascular allograft rejection. Antigens expressed by the endothelium can act to promote and be the target of rejection reactions, which often lead to thrombosis and ischemic necrosis of the allograft. In this study, segments of femoral artery and femoral vein with or without endothelium were grafted between allogenic or autologous control rats. Immunocompetent Lewis ($RT1^{l}$) recipient rats were randomly selected for groups (N = 14 for each) receiving the following: ACI^{-} ($RT1^{a}$) allografts with intact endothelium, allografts with endothelium removed before operation, autografts with endothelium, and autografts with endothelium removed. Rejection was assessed by graft patency as well as morphologic and ultrastructural changes. At 5 days, the allografts with intact endothelium were totally occluded, whereas allografts without endothelium remained patent, as did autologous control grafts with or without endothelium. Two additional groups (N = 14 each) receiving the de-endothelialized allografts or autografts were examined at 120 days after operation, revealing that grafts in both groups were still patent and had been re-endothelialized. These findings indicate that physical removal of vascular endothelium may depress vessel allograft rejection without immunosuppressive therapy.

DESPITE SIGNIFICANT ADVANCES in the field of transplantation, the rejection phenomenon remains the major cause of graft failure. Previous investigations assessing rejection in renal allografts,[1] cardiac allografts,[2] and cutaneous allografts[3] have reported that graft failure may often occur as a result of vascular rejection, especially after presensitization to antigens expressed on the vascular endothelium. This rejection manifests itself as endothelial destruction, with subsequent luminal thrombus formation and graft occlusion. Allograft endothelial destruction is initiated by surface antigens encoded by the major histocompatability complex (MHC), as well as blood groups and other antigen systems.[4,5] In addition to expressing these antigens, which can stimulate and act as targets for immune responses, vascular endothelium may directly express inflammatory mediators that can promote the activation of T cells,[6] which are the major immune effectors in acute rejection.[6,7]

In an attempt to arrest acute rejection, immunosuppressive agents have been employed in allograft transplantation. However, many of these agents lead to serious complications and death in the host.[8] Newer agents, such as cyclosporin A, effectively diminish the host immune response to allograft transplantation, yet current investigations reveal that once the immunosuppressive agents are discontinued, the host immune response often becomes reactivated, leading to allograft rejection.[9]

In this investigation attempts were made to alter vascular allograft rejection in immunocompetent animals without the use of immunosuppressive agents. Removal of the vascular allograft endothelium before graft insertion resulted in long-term patency, and de-endothelialized allografts were found to be resurfaced with cells structurally and phenotypically similar to endothelium.

Materials and Methods

Vascular Transplantation

MHC-disparate rats, ACI ($RT1^{a}$), and Lewis ($RT1^{l}$) were used. All animals were males weighing between 195 and 200 g and were obtained from Harlan Sprague

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Supported in part by NIH Grant A1 19368 (F.P.S.) and HL-15448 (P-O. H.).

Reprint requests and correspondence: Mr. Anthony V. Seaber, Department of Surgery, P.O. Box 3093, Duke University Medical Center, Durham, NC 27710.

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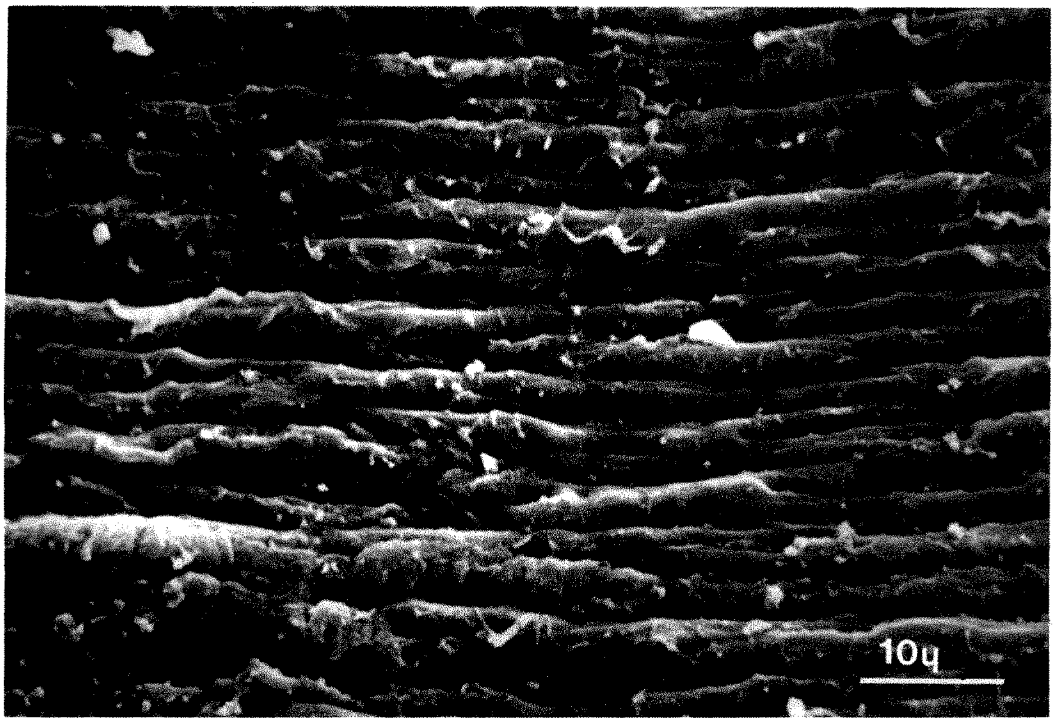

FIG. 1. Scanning electron micrograph of de-endothelialized artery. Rotating the vessel lumen around a 1-mm dilator removes endothelium without causing damage to the media. (Original magnification ×23,000.)

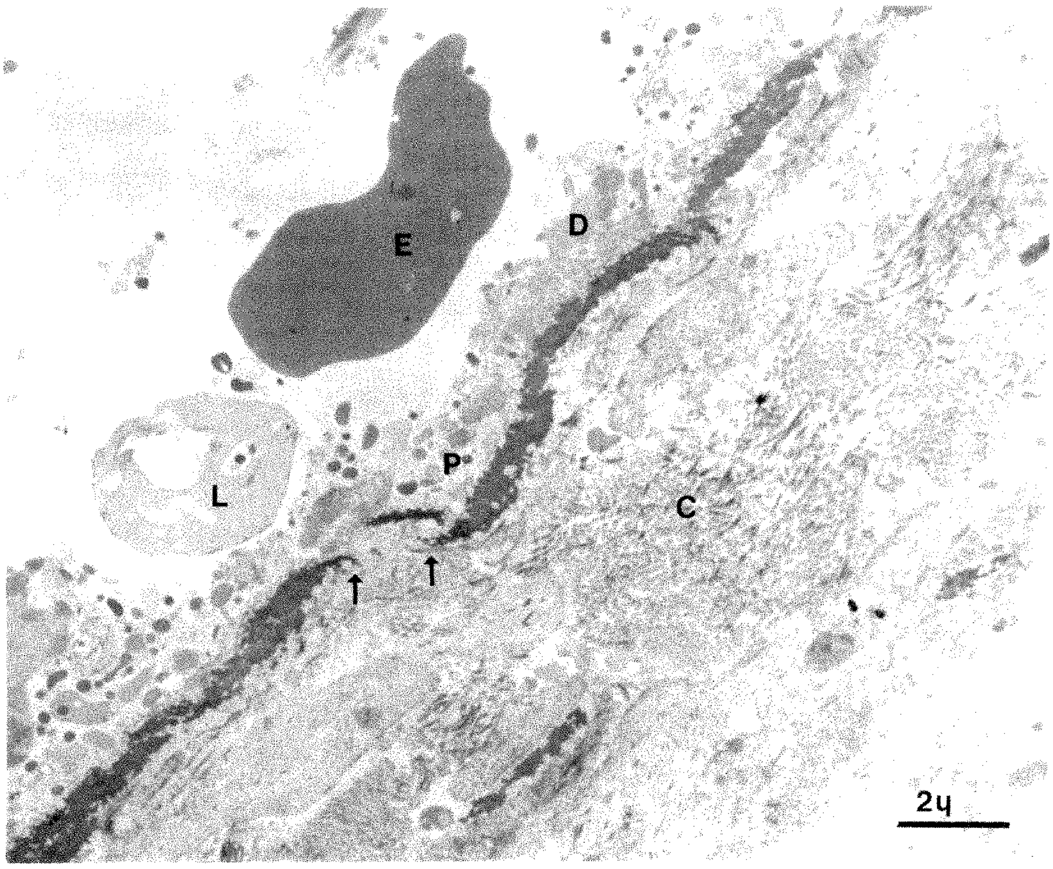

FIG. 2. Transmission electron micrograph of a venous allograft 5 days after transplantation. The lumen contains erythrocytes (E), leukocytes (L), platelets (P), and cellular debris (D). Endothelial cells have been destroyed, and disruption of the internal elastic membrane (IEL) (arrows) has occurred. Beneath the IEL is collagen (C). (Original magnification ×10,000.)

TABLE 1. *Graft Patency after Endothelial Manipulation with Two-forceps Technique*

		Allograft		Autograft	
Time	Vessel	Endothelium	No Endothelium	Endothelium	No Endothelium
5 days	Artery	0/14 (0%)*	14/14 (100%)	13/14 (93%)	14/14 (100%)
5 days	Vein	0/14 (0%)*	13/14 (93%)	14/14 (100%)	14/14 (100%)
120 days	Artery		14/14 (100%)		14/14 (100%)

* Indicates significant difference from controls $p < 0.05$.

Dawley. Grafts used were 1-cm portions of femoral artery and vein harvested between the inguinal ligament and the profunda femora vessel of the donor rat. Before operation, all rats received 200 U/kg of porcine heparin intraperitoneally (I.P.). The rats were anesthetized with pentobarbital (Nembutol®, Abbott Laboratories, North Chicago, IL) (60 mg/kg I.P.). All operative procedures were conducted under sterile conditions. The donor site was exposed, as was the host vascular bed. The graft was then excised by use of the operating microscope and standard microsurgical instrumentation. The graft was immediately transplanted into the host femoral vessel (artery to artery, vein to vein) by use of the Microsurgical Triple Clamp, previously described.[10] The wound was closed with 3-0 dexamethasone sodium phosphate (Dexon, Kay, Tulsa, OK), and the animal was returned to the housing facility and cared for according to National Institutes of Health guidelines.

Endothelial Removal

Endothelium was removed by placing a 1-mm metal dilator inside the arterial and venous lumina. The vessel was then rotated around the dilator, and the dilator was removed. Scanning electron micrographs revealed complete endothelial removal without damage to the media (Fig. 1). Comparable mechanical procedures to de-endothelialize arteries and veins have revealed similar results.[11,12]

Experimental Groupings

Eighty-four Lewis rats were randomized equally into six groups. Group 1 consisted of ACI donor femoral artery and vein segments transplanted into Lewis rats, referred to as allograft—endothelium intact. Group 2 consisted of Lewis artery and vein autografts, referred to as autograft—endothelium intact. Group 3 consisted of ACI donor femoral artery and vein segments, with the endothelium mechanically removed before being transplanted into Lewis rats, referred to as allograft—endothelium removed. Group 4 consisted of Lewis artery and vein autografts in which the endothelium was mechanically removed, referred to as autograft—endothelium removed. Group 5 consisted of ACI donor femoral artery segments that had the endothelium mechanically removed, transplanted into Lewis rats, and held for 120 days, referred to as long-term allograft—endothelium removed. Group 6 consisted of Lewis artery autografts held for 120 days, in which the endothelium was mechanically removed and referred to as long-term autograft—endothelium removed.

Postoperative Graft Harvesting, Colloid Carbon Tracer Injection, and Fixation Procedures

Five days after operation, the host rats in groups 1–4 were anesthetized with pentobarbital I.P. The operative

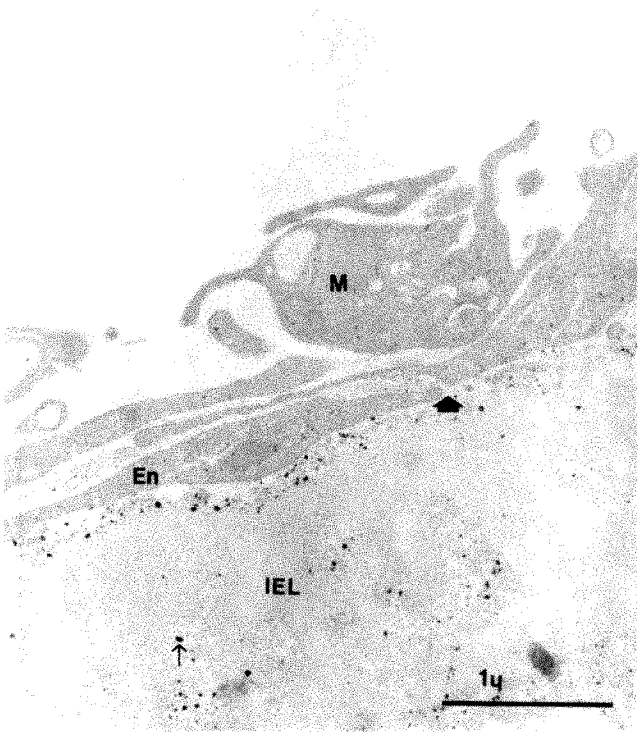

FIG. 3. Transmission electron micrograph of an arterial allograft 5 days after transplantation. Macrophage (M) is juxtaposed to hypertrophic endothelial cells (En), which are separated by endothelial gaps (arrowhead). Carbon particles (arrow) are present throughout the internal elastic membrane (IEL). (Original magnification ×30,000.)

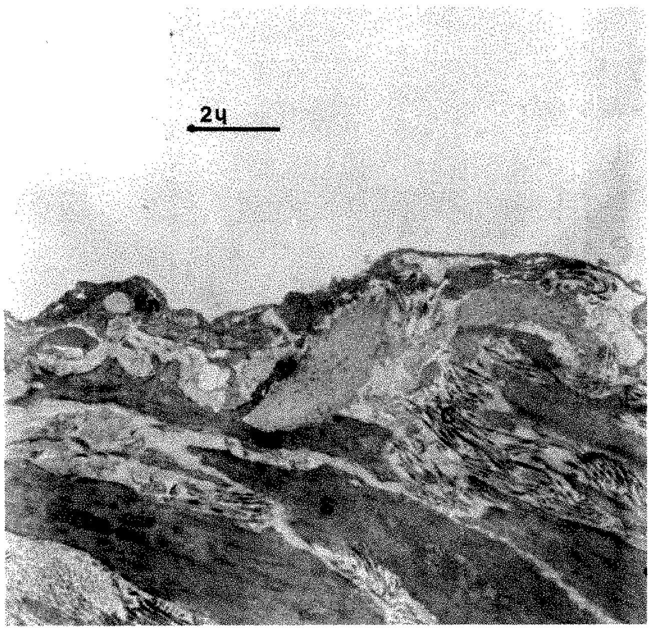

FIG. 4. Transmission electron micrograph of an arterial autograft 5 days after transplantation. Endothelium (En) is intact. Notice bundles of smooth muscle (S) and collagen (C). (Original magnification ×8500.)

site was re-exposed, and the graft was tested for patency by use of the two-forceps test. The rat was then injected with 2.5 mL of a 10% colloid carbon solution into the femoral vein, contralateral to the operated side.[13,14] Thirty minutes after tracer injection, a cannula was introduced into the abdominal aorta, and the rats were perfused with a 10 mM Hepes buffer solution at 10 cm H_2O for 5 minutes. This was followed by perfusion of a 0.1 sodium cacodylate buffer with 5% sucrose for 5 minutes, followed by a 3% gluteraldehyde in 0.1 M sodium cacodylate perfusion for 5 minutes. The grafts were then removed, placed in vials, coded, and processed for the scanning and transmission electron microscopes by use of previously described techniques for vascular fixation.[15,16] The vessels were then assessed by Jeol JSM-35E (Jeol, Peabody, MA) scanning and Philips 301 (Phillips Electronic Inc., Mahwah, NJ) transmission electron microscopes. The tissues were assessed in a masked fashion for changes in the vessel lumen, as well as endothelial ultrastructural morphologic characteristics and patterns of colloid carbon vascular distribution. Rats in groups 5 and 6 were harvested at 120 days and processed in a similar manner.

Immunoperoxidase Labeling

Frozen sections of fresh graft specimens were labeled with monoclonal antibodies to rat leukocyte common antigen (OX-1), rat T cells (OX-19), rat T helper cells (W3/25), and rat T cytotoxic/suppressor cells (OX-8) and polyclonal antibodies to factor VIII–related antigen

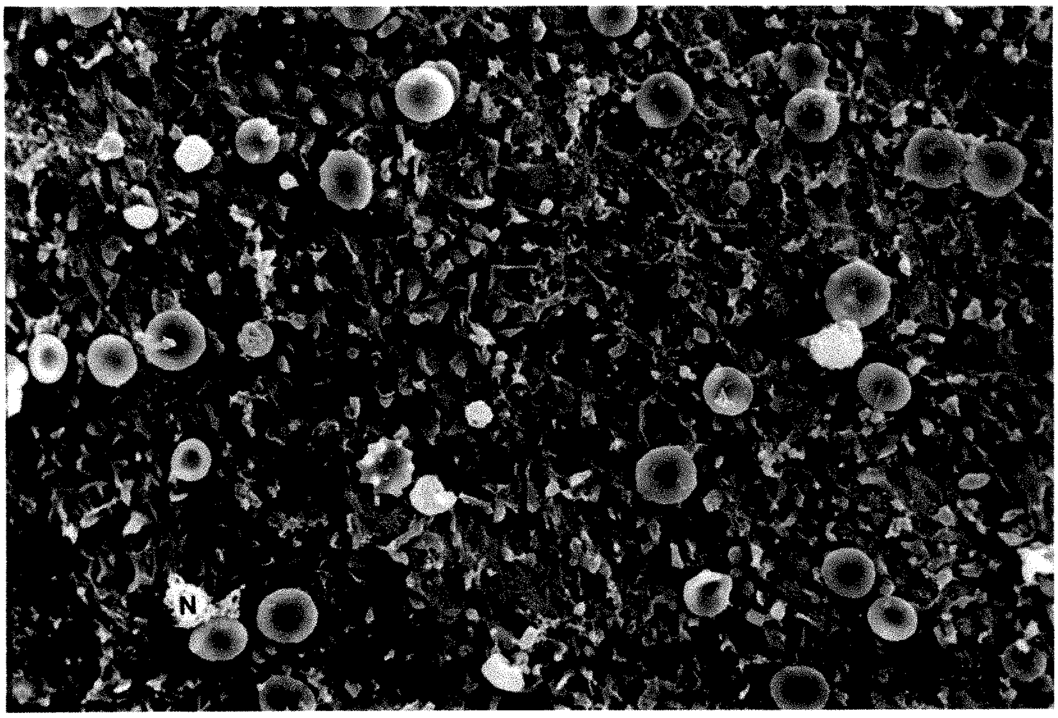

FIG. 5. Scanning electron micrograph of de-endothelialized arterial allograft 5 days after transplantation. Present on the vessel surface are erythrocytes (E), neutrophils (N), platelets (P), and fibrin (arrow). (Original magnification ×1400.)

and vascular smooth muscle myosin, as previously described.[17,18]

Statistical Analysis

Student's t-test was used to determine significance.

Results

Graft Function (Table 1)

Group 1 (allograft—endothelium intact). No arteries or veins were patent at 5 days. All vessels had areas of clot within the vessel lumina. These clots ranged from partial to total transmural obstruction of the graft.

Group 2 (autograft—endothelium intact). All arteries were patent, and 13 of the 14 veins were patent. One vein was occluded because of poor anastomotic technique.

Group 3 (allograft—endothelium removed). Thirteen of 14 arteries were patent, and all 14 veins were patent. The arterial occlusion resulted from poor anastomotic technique.

Group 4 (autograft—endothelium removed). All vessels were patent.

Group 5 (long-term allograft—endothelium removed). All vessels were patent.

Group 6 (long-term autograft—endothelium removed). All vessels were patent.

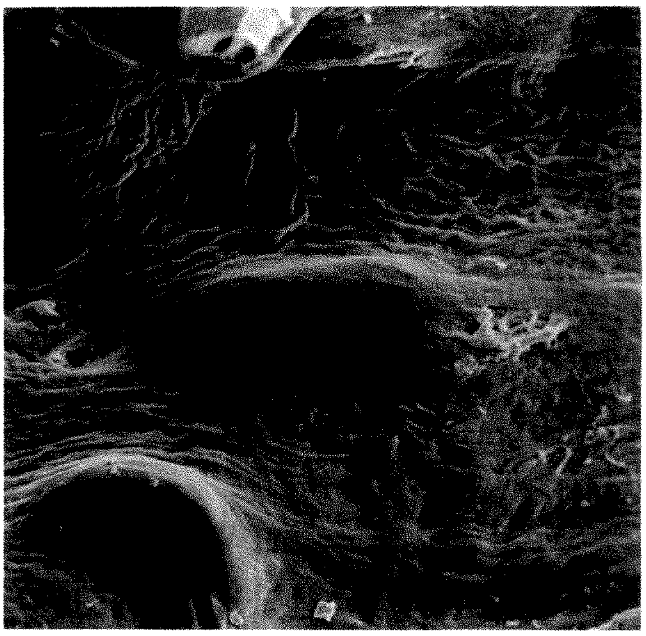

FIG. 6. Scanning electron micrograph of a 120-day arterial allograft. The luminal surface is covered by a monomorphic layer of cells resembling endothelial cells. (Original magnification ×750.)

Ultrastructural Changes

Group 1 (allograft—endothelium intact). Luminal contents included erythrocytes, platelets, and lympho-

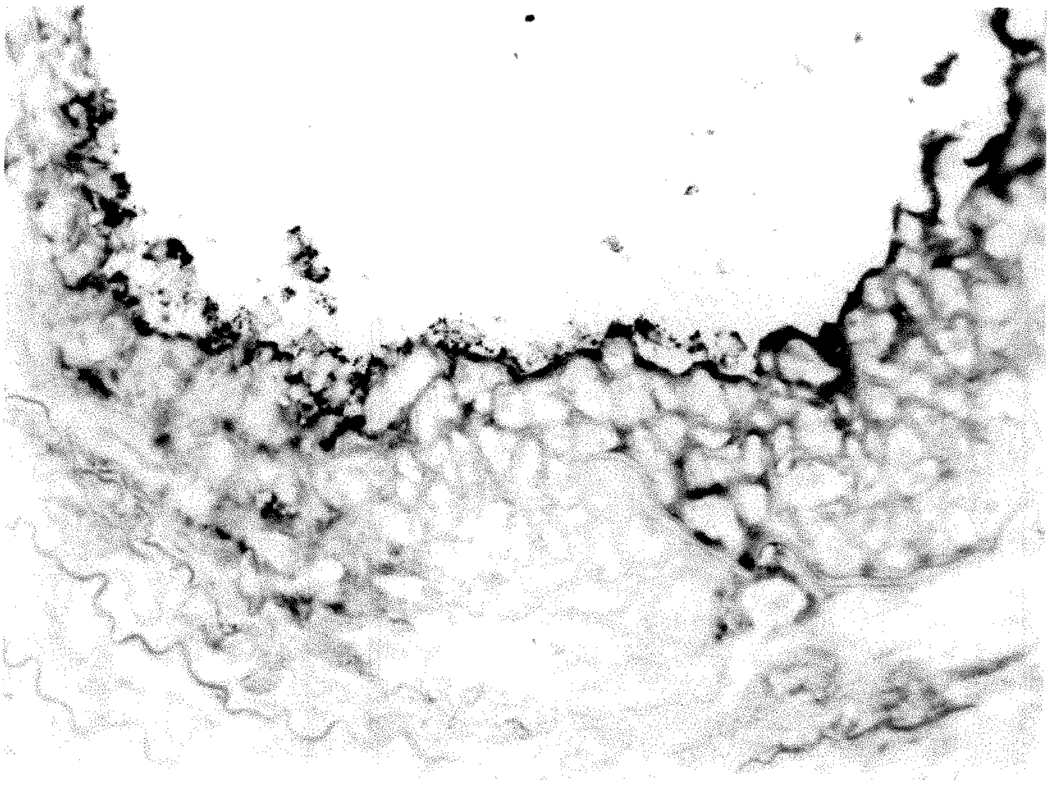

FIG. 7. Immunoperoxidase labeling of a 120-day arterial allograft using anti-factor VIII-related antigen. The luminal surface monolayer of cells is positively stained. (Original magnification ×450.)

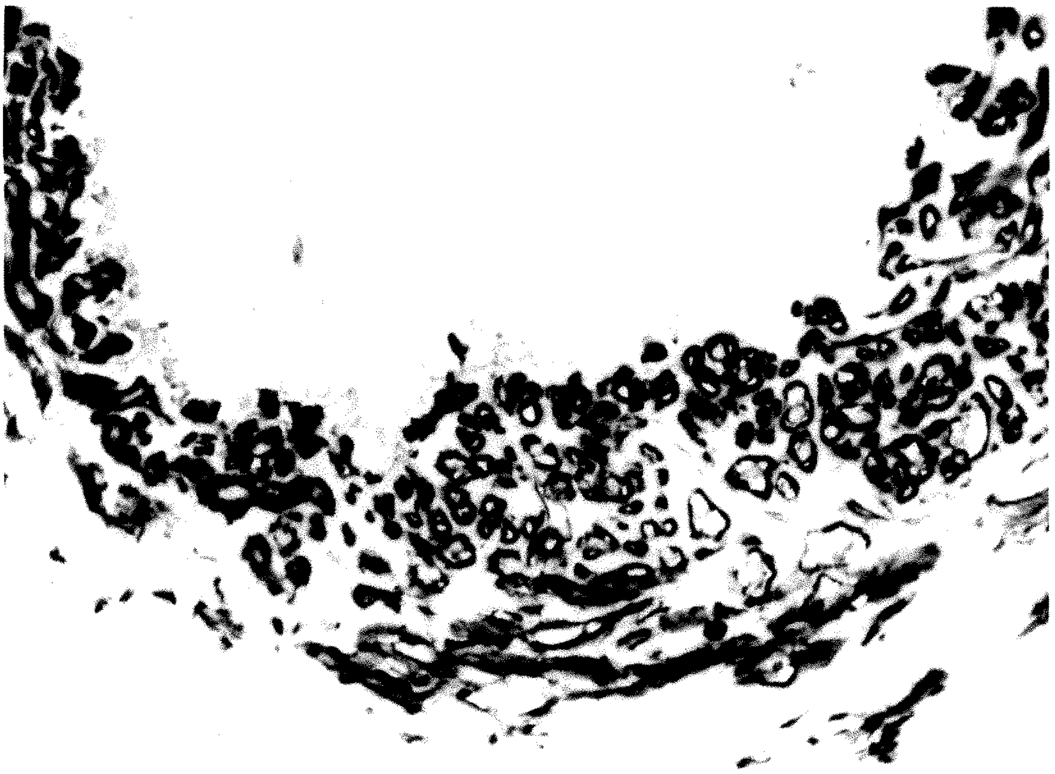

FIG. 8. Immunoperoxidase labeling of a 120-day arterial allograft with the use of anti-smooth muscle myosin. The muscularis had positive results, whereas the luminal monolayer had negative results. (Original magnification ×450.)

cytes enmeshed in fibrin and cellular debris (Fig. 2). Macrophages appeared to marginate from the lumen and invade the vessel wall (Fig. 3). Extensive segments of denuded endothelium were present. Where endothelial cells did exist, they were separated by interendothelial gaps. The endothelium appeared to be hypertrophic and contained multiple vesicular bodies. Colloid carbon tracer was present subintimally, suggesting destruction of the basement membrane.

Group 2 (autograft—endothelium intact). In this group arteries and veins showed no vascular alterations when compared with the host's own unoperated vessels. Normal endothelia with competent interendothelial junctions were present (Fig. 4). Carbon tracer was not subintimal, suggesting an intact basement membrane.

Group 3 (allograft—endothelium removed). As the endothelium was removed before operation, the subintimal surface was covered with a meshwork of fibrin strands, in which platelets, erythrocytes, and neutrophils were observed (Fig. 5). There was no evidence of intraluminal clot. Carbon tracer was present subintimally.

Group 4 (autograft—endothelium removed). Ultrastructurally the surfaces of these arteries and veins appeared similar to those of group 3. A fibrin meshwork covered the subintimal surface, in which platelets, erythrocytes, and neutrophils were observed. Intraluminal clot was not present, and carbon tracer was seen subintimally.

Group 5 (long-term allograft—endothelium removed). The luminal surface was covered with a monomorphic layer of cells, resembling endothelium (Fig. 6). Intraluminal clot was not present, and carbon tracer was not present subintimally.

Group 6 (long-term autograft—endothelium removed). Ultrastructurally, the luminal surfaces of these arteries appeared indistinguishable from those of group 5. A monomorphic layer of cells covered the luminal surface. Intraluminal clot was not present, and carbon tracer was not seen subintimally.

Lymphocyte Infiltrates

Representative specimens of arterial and venous grafts from each of the four groups were examined for the presence of leukocyte infiltrates and T cell subsets by immunoperoxidase labeling with monoclonal antibody. No significant infiltrates were seen in autografts with an intact endothelium, whereas a mild intravascular infiltrate was seen in autografts with the endothelium removed. Occluded arterial and venous allografts with an intact endothelium both showed a mild–moderate infiltrate that was greater in the muscularis than the adventitia and had equivalent infiltrates of OX-8 and W3/25-positive T cell subsets. Patent arterial and venous allografts with removed endothelium also showed moderate T cell infiltrates of the same pattern and distribution as allografts with an intact endothelium. Sampling of grafts from Groups 5 and 6 (long-term allografts and autografts with removed endothelium) revealed the presence of a monomorphic layer of cells that showed positive labeling with anti-factor VIII-related antigen (Fig. 7) and negative staining with anti-vascular smooth muscle myosin (Fig. 8). Staining results for rat MHC antigens of donor ACI (R2/10P) and recipient Lewis (OX3) strains were negative for the former and equivocal for the latter.

Discussion

Current theory of vascular rejection suggests that allograft endothelial surface antigens serve as a stimulus to initiate host immune responses.[19] These surface antigens include MHC gene products such as class I and class II antigens, as well as non-MHC antigens, such as blood group and endothelial-monocyte antigens.[20,21] These alloantigens attract various mediators of the host immune response, especially cytotoxic T-cells, helper/suppressor T cells, and macrophages.[22,23] Our results show that vascular allografts with an intact endothelium become occluded, whereas vascular allografts without endothelium remain patent.

Evidence for endothelial rejection, thrombus formation, and graft occlusion has been based on observations in organ transplantation. However, rejection of a vascular allograft has not been described. This study shows that vascular allografts undergo changes similar to those seen with organ transplants. These ultrastructural changes include destruction of the endothelium and basement membrane, resulting in thrombus formation and graft occlusion. Similarly, the cellular infiltrates observed in preliminary immunopathologic analysis are consistent with infiltrates seen during rejection of organ transplants.

Previous studies have shown that in subjects given heparin before operation, de-endothelialized vessels become covered with a thin layer of platelets, erythrocytes, and other blood elements.[24] Within several days this surface becomes nonthrombogenic. Inflammatory cells, macrophages, and neutrophils, but apparently not lymphocytes, infiltrate the media of these vessels.[25] Simultaneously, endothelium adjacent to the area of injury begins to multiply and migrate, eventually covering the de-endothelialized portion of the vessel.[26]

Our study suggests that a similar process occurs with endothelial removal in allografts. Within 1 week after endothelial removal, allografts appeared to be covered with platelets, erythrocytes, neutrophils, and fibrin. Immunopathologic observations suggest that the de-endothelialized allografts are associated with an inflammatory response but, unlike autografts, are infiltrated with T cells. Moreover, unlike the allografts with endothelium, the vessels remained patent. Patent allografts harvested at 120 days after operation revealed that the luminal surface is covered by a monomorphic layer of cells ultrastructurally similar to endothelium. Further, these cells stained positively for factor VIII and had negative results for vascular smooth muscle myosin, also suggesting that they were endothelial in origin and probably host derived.

Although vascular allografts with and without endothelium have similar cellular infiltrates, endothelial removal precludes endothelial rejection and resultant thrombus formation. This alteration of acute rejection maintains vascular patency, ultimately resulting in resurfacing of the allograft vessel with host endothelium. These findings suggest that endothelial manipulation and appropriate anticoagulation in the absence of immunosuppressive therapy may provide a means of using nonautologous vessels for vascular replacement surgery.

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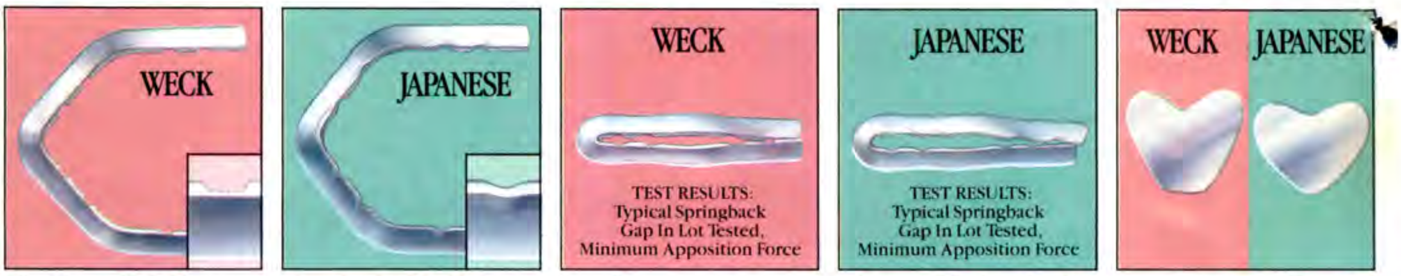


The Hemoclip® ligating clip is coined with distinct rectangular transverse grooves, designed for longitudinal gripping power. Clip wire is processed metallurgially for malleability in closure. The Japanese imitation clips have shallow-drawn wire, and smaller, rounded transverse grooves. Deeper Hemoclip® wire shape aids retention in Weck appliers. (Typical closure illustrated from independent study.)

But now there's a problem you should be aware of. Some U.S.-based companies have begun distributing–not manufacturing–Japanese imitations of the Hemoclip® ligating clip. These clips are not the product of Weck manufacturing expertise and the technical performance of these clips is simply not the same as that of Hemoclip® ligating clips, an exclusive Weck product.

They may look the same, but they're not.

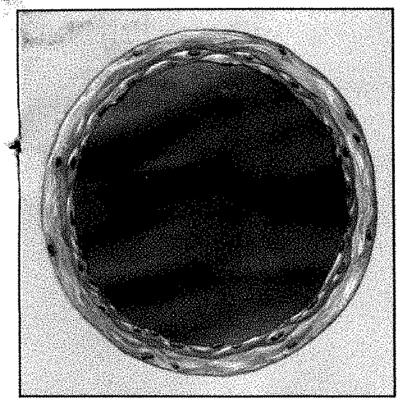
The recently-introduced Japanese clips look the same as Hemoclip® ligating clips to the naked eye. But a recently completed independent lab study of sample quantities of clips confirms Weck's own observation of substantial differences in closure properties between the Japanese clips and Weck clips.

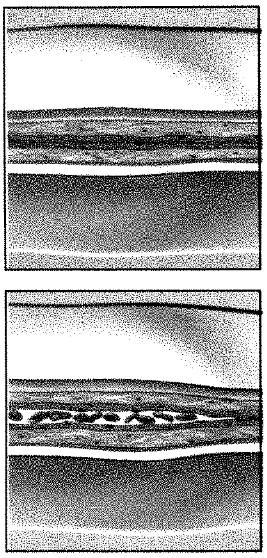
Vessel walls may be as thin as one-twelfth of vessel diameter.

Veins, in contrast to arteries, have very thin walls. When you consider that the vein tributaries ligated in surgery are sometimes one millimeter in diameter or smaller, with combined vessel walls as small as seven-thousandths of an inch (178 microns), according to animal studies on comparable vessels, you can appreciate the functional importance of differences in closure gap.

Arterial tributaries can be tiny, too, and although their walls are generally thicker than vein walls, arterial pressure is higher than venous pressure.

It seems prudent to employ ligating clips which offer the response and clip-closure performance Weck usage has established in your surgery.





ABOVE. A vein tributary of 1mm can have a combined wall thickness of just seven-thousandths of an inch (178 microns), according to animal studies. RIGHT. A ligating clip that demonstrates greater springback than the clip you have regularly used for such vessels may be more likely to leave a closure gap larger than the vessel-wall thickness of a tiny vessel.

Weck's titanium clip vs. their titanium clip. A 23-27% difference.

Examine the chart for a visual representation of the difference in closure springback an independent research firm discovered between a set of Weck titanium medium-size clips and a set of Japanese titanium medium-size clips obtained directly from U.S. distributors of those clips. Both sets of clips were closed in Weck appliers through use of force-control devices.

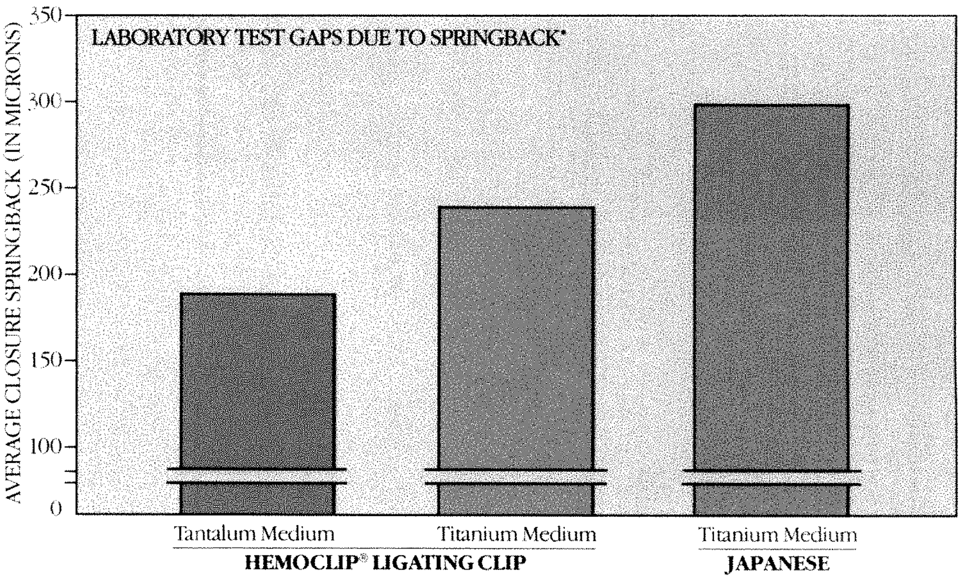
Closure of two sample sets of 25 Japanese titanium medium clips at forces adequate to achieve initial complete touching along clip legs resulted in closures of about 12 thousandths of an inch (305 microns) for the Japanese clips, 23-27% larger than the Weck titanium clip closure gap.

Weck's tantalum clips vs. their titanium clips. A 56% springback difference.

The comparison of Japanese titanium with Weck tantalum clips is even more important.

The Japanese companies make only titanium clips, and so they have sold hard on the benefits of titanium.

Tantalum is a softer material known for excellent clip closure. And the study revealed 56% and 61% larger mean closure gaps after springback for two sets of Japanese titanium clips, a ringing endorsement of the closure advantages of the Weck tantalum clips tested.



An independent lab study on two sample sets of 25 Japanese imitation clips vs. Weck clips found that the Japanese medium-size clips, closed to initial complete touching of clip legs, evidenced mean closure gaps, due to springback, 23-27% larger than Weck medium-size titanium clips, and 56-61% larger than Hemoclip® tantalum clips from Weck. Other sizes produced similar results. (Closure gap in microns-one micron = one thousandth of one millimeter).

**Stronger closure forces would likely be employed during actual surgery cases.*

The comparison was similar for Weck stainless vs. Japanese titanium, with the stainless scoring substantially smaller gaps after springback.

Odds are, if you are using Weck clips you are accustomed to tantalum or stainless steel clip closure, because the vast majority of Weck accounts use these two metals.

And a new Weck-funded NMR major-university study indicates that magnetic deflection of tantalum clips is negligible, just as it is for titanium clips. So if your local competitive salesman distributing Japanese clips tries to convince you that titanium clips are exclusively acceptable for NMR magnetic deflection in preference to tantalum, we suggest you cite the new Weck-sponsored university study.

Look for the Weck name on the cartridge.

To visually and quickly confirm that you really are using Weck clips, look at the end of the clip cartridge. If you are using Weck clips, you should see there the Weck name molded into the plastic. The Weck name is your assurance of genuine Hemoclip® clip processing experience and knowledge.

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Repair of Large Abdominal Wall Defects with Expanded Polytetrafluoroethylene (PTFE)

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Most abdominal wall incisional hernias can be repaired by primary closure. However, where the defect is large or there is tension on the closure, the use of a prosthetic material is indicated. Expanded polytetrafluoroethylene (PTFE) patches were used to repair incisional hernias in 28 patients between November 1983 and December 1986. Twelve of these patients (43%) had a prior failure of a primary repair. Reherniation occurred in three patients (10.7%). Wound infections developed in two patients (7.1%), both of whom had existing intestinal stomas, one with an intercurrent pelvic abscess. The prosthetic patch was removed in the patient with the abscess, but the infection was resolved in the other without sequelae. Septic complications did not occur after any operations performed in uncontaminated fields. None of the patients exhibited any undue discomfort, wound pain, erythema, or induration. Complications related to adhesions, erosion of the patch material into the viscera, bowel obstruction, or fistula formation did not occur. Based on this clinical experience, the authors believe that the PTFE patch appears to represent an advance in synthetic abdominal wall substitutes.

THE MANAGEMENT of major abdominal wall defects or incisional hernias continues to be a fundamental problem for surgeons. Primary musculofascial repair is sufficient for most patients. There are, however, refractory cases where the use of a prosthetic material is indicated. During the course of this century, many materials have been tried with such variable results that skepticism exists among surgeons regarding the role of *any* prosthetic material in abdominal wall repair.

In an extensive review of the literature, Poole[1] found the incidence of abdominal incisional hernia to from 1 to 3%. A recent British study that followed patients up to 10 years after abdominal surgery reported an 11% incidence of incisional hernia, with most occurring within 3 years after operation.[2] The rate of incisional hernia after primary closure undoubtedly varies widely among surgical centers because of differences in surgical technique and patient population. Once herniation through the abdominal wall has occurred, studies indicate that 30% of patients who have repair without the use of a prosthetic patch will have a recurrence.[3,4]

A variety of prosthetic materials have been used for abdominal wall replacement with equivocal results. Complications of synthetic materials have been largely related to the intrinsic tendency of the materials to promote inflammation or serve as a nidus for infection. Theoretically, the ideal synthetic fascial substitute would be strong, biologically inert, noncarcinogenic, and stable in the presence of infection. Expanded polytetrafluoroethylene (PTFE) material appeared to meet these criteria. We report our experience with the recently developed expanded PTFE patch (GORE-TEX Soft Tissue Patch, W. L. Gore and Associates, Inc., Flagstaff, AZ) in a group of patients who had incisional hernias or abdominal wall defects of such magnitude as to preclude primary repair without prosthetic materials.

Clinical Material

Ninety-one incisional hernia repairs were performed by the authors at the Mount Sinai Hospital, New York, between November 1983 and December 1986. Repairs requiring the use of a prosthetic patch were performed in 28 patients (30.8%). There were 13 men and 15 women in this group, with an average age of 56 years (range: 27–79 years). Twelve patients (42.9%) had at least one previous repair of the incisional hernia. Of the hernias requiring a prosthetic patch, nine were associated with failed midline incisions, eight were present at prior os-

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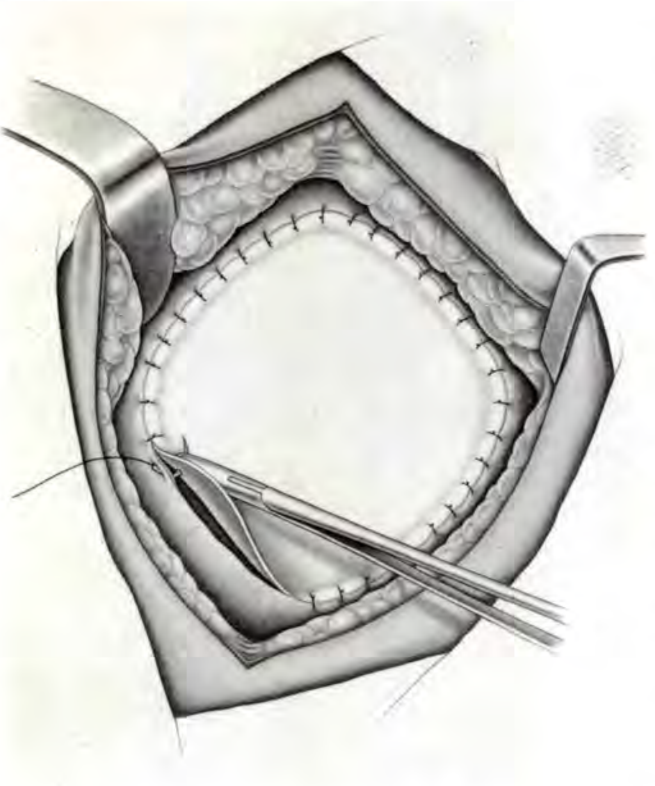


FIG. 1. Full-thickness implant of expanded PTFE patch in the tension-free repair of abdominal incisional hernia.

tomy sites, three involved failed flank incisions, and two were associated with incisions made for spinal fusion, with the balance at various other points in the abdominal wall. Only one defect was associated with a tumor (ovarian) that had infiltrated the substance of the abdominal wall. The dimensions of the hernias repaired with patch material varied between 5 × 8 cm and 12 × 20 cm.

Methods

A broad-spectrum antibiotic was administered to patients 6 hours before operation. Two patients had existing intestinal stomas, and one of these had an intercurrent pelvic abscess. The remaining 26 operations were performed in a clean, uncontaminated field.

After skin preparation with a povidone–iodine solution, the fascial margins of the incisional hernia were identified. The peritoneal cavity was entered, and any loops of intestine adherent to the parietal peritoneum near the fascial margin were dissected free to avoid injury to the bowel during the reconstruction. At this point, tension on the wound was assessed and, if a tension-free repair could be performed, the wound was closed with interrupted sutures. If not, an appropriately sized expanded PTFE patch of 2 mm thickness was implanted.

The prosthetic patches were trimmed to bridge the tissue defect. No attempt was made to re-establish the peritoneum between the prosthetic patch and the underlying viscera. The patch was sutured to the fascial margins with the use of interrupted number 0 polypropylene sutures. All sutures were placed 2–3 mm from the edge of the prosthetic patch. The patch was tailored so that normal abdominal contours were reconstituted while minimal tension was placed on the repair (Fig. 1). No drains of any kind were used.

Antibiotic administration was terminated 5 days after operation unless there was evidence of wound infection. The surgical wounds were inspected daily for general state of healing and any evidence of infection, erythema, induration, tenderness, seroma, hematoma, or abscess formation. Patients were walking on the first day after operation, fed when intestinal function resumed, and normally discharged from the hospital within 7 days. Patients were seen at 3- to 4-month intervals during the first postoperative year and at yearly intervals thereafter. No patients were lost to follow-up.

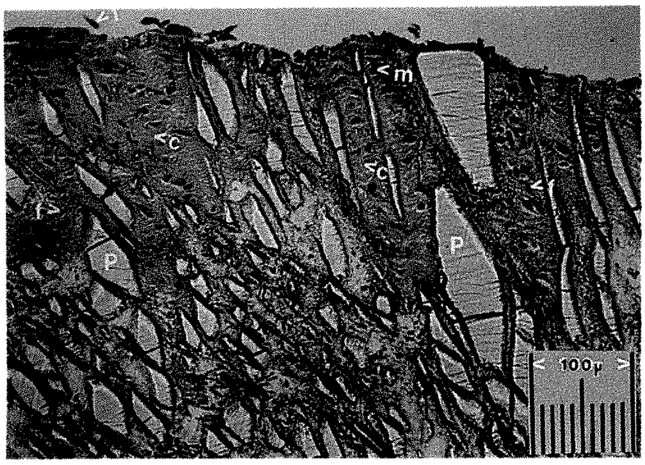
Results

Mean follow-up of patients receiving expanded PTFE patches was 22.5 months (range: 3.5–38 months). Twenty-three of the 28 patients (82%) had an uneventful postoperative course. None of these 23 patients demonstrated any adverse tissue reaction to the PTFE material. Erythema, edema, induration, and excessive pain at the operative site were not seen.

Reherniation occurred in three patients. These recurrences were noted at 3, 4, and 9 months after operation. The patient in whom a recurrence developed at 3 months was the only one who elected to return for reoperation. When this wound was explored 5 months after the original operation, a single polypropylene suture at the recurrence site was found lying free and untied in the subcutaneous scar tissue. This had allowed the fascia/patch interface to separate at its lateral inferior margin. A biopsy revealed firmly adherent fibrous tissue on the anterior surface of the patch. Fibroblasts were found within the interstices of the material, and collagen had penetrated into the anterior surface of the patch for a mean distance of 200 μm, demonstrating good healing within the 5-month period of implant. A minimal inflammatory response was noted (Fig. 2).

The remaining two recurrences were in patients who had previous repairs for incisional hernia. One of these also had undiagnosed liver disease and drained ascitic fluid through the wound for 5 days after operation.

Postoperative wound infections developed in two pa-



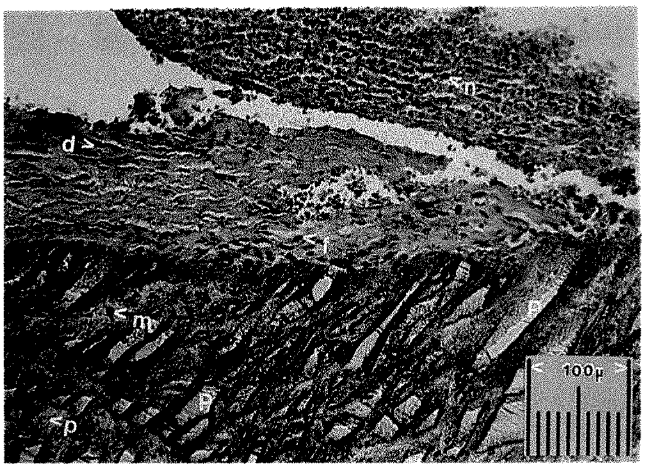


FIG. 2 (*left*). Biopsy specimen of expanded PTFE patch material obtained during reoperation for recurrent hernia. Good fibroblastic and collagen penetration is noted beneath healthy fibrous tissue on surface. f = fibroblast, c = collagen, m = macrophage, P = PTFE (node). (Hematoxylin and eosin stain, original magnification ×50.) FIG. 3 (*right*). Expanded PTFE patch removed from infection site. The patch material was covered (top) by a small fragment of fibrous tissue and a granular protein-neutrophil-erythrocyte matrix. Beneath the healthy tissue (center), slight infiltration of fibroblasts into the patch wall was evident. The remainder of the interstices was filled with thin granular protein. f = fibroblast, m = macrophage, n = neutrophil, p = protein, P = PTFE (node), d = degenerated cell mass. (Hematoxylin and eosin stain, original magnification ×50.)

tients. One patient, operated on for a massive parastomal hernia, had a low-grade wound infection that resolved with local and systemic antibiotic treatment. The sinus in this patient drained intermittently for 4 months but has now been closed for 3 months. In the other patient, the expanded PTFE patch, placed in the presence of multiple abdominal stomas and a pelvic abscess, became grossly infected. Attempts were made to salvage the patch, but after 10 days of local antibiotic, topical povidone–iodine treatment, and tissue debridement the patch was removed. There was a large amount of purulent exudate beneath it. Cultures revealed a variety of enteric organisms. After explantation, the wound healed well and eventually closed, leaving the patient with a large ventral hernia.

Histologic analysis of the explanted patch revealed slight healing at the suture line associated with a minimal inflammatory response. The remainder of the expanded PTFE material showed a degenerated cellular protein matrix usually associated with infection (Fig. 3).

Discussion

The lack of suitable musculofascial tissue in the proximity of the abdominal wall that can be used to repair defects has led to the use of synthetic prostheses when tension-free approximation of abdominal musculofascial tissues cannot be achieved. Abdominal wall reconstruction is, in fact, one of the few areas of surgical practice where the use of synthetic prostheses antedated the use of autologous tissue. Silver mesh was employed in Germany at the end of the last century[5,6] and was adopted in the United States by 1903.[7] Unfortunately, silver was found to corrode when in contact with tissue fluids and was replaced by mesh fabricated from the inert metal tantalum in 1940.[8]

The tendency of tantalum to fragment after repeated flexion in the tissues[9–11] was recognized before the 1950s, but the serious complications of small bowel fistula, ulceration, and erosion of metal fragments through the skin and peritoneum were not reported until the 1960s.[12–14] A variety of synthetic polymers discovered in the late 1950s and early 1960s soon became available for use in abdominal wall replacement. Two prosthetic mesh materials used in ventral hernia repair at the present time, polypropylene[15] (Marlex [C. R. Bard, Inc., Murray Hill, NJ], Prolene [Ethicon Inc., Summerville, NY]) and Dacron[16] (Mersilene [Ethicon Inc.]), date from this period. A third material, PTFE (Teflon, DuPont, Wilmington, DE), appeared promising in animal studies,[17] but clinical experience with mesh woven from solid Teflon fiber was so unfavorable[18] that its use was all but abandoned. With the discovery in the 1970s of a process to expand Teflon polymers into a porous form[19] (expanded PTFE), it once again became useful as a prosthetic material.[20]

Polypropylene has been the most widely used prosthetic patch material used in the repair of hernias[21] since its formulation and testing by Usher in 1963.[15] However, the clinical experience with polypropylene mesh has been replete with a variety of complications, such as wound sepsis,[22] erosion into intra-abdominal organs,[23] bowel fistula,[22,24,25] and mesh extrusion.[25] After review of the clinical and experimental data on expanded PTFE prostheses, it became apparent that the expanded PTFE material possessed several advantages, namely (1) it elicits a low foreign body reaction[26]; (2) it has low infectability[27,28]; (3) it exhibits a low rate of adhesion formation[29]; and (4) supports fibrous tissue incorporation.[30] In addition, expanded PTFE sheet material is soft and flexible and has been reported to produce a more aesthetic result with less patient discomfort when reconstituting abdominal contour.[31] These physical characteristics also reduce any tendency by the material to provoke sinus formation or erode into the abdominal viscera, leading to fistulae.

Prosthetic materials are employed during the repair of abdominal wall defects to avoid closure of the wound under excess tension, which might result in recurrent incisional hernia. In this series of patients, we have experienced three recurrent hernias, for an overall recurrence rate of 10.7%. One of the three was related to failure of a suture. The other two occurred in patients who had at least one prior recurrence, but the reason for the failure of their present repair is unknown. These results compare favorably with a recent study, using full-thickness placement of polypropylene mesh, that reported a 12% recurrence rate within 3 years of operation.[4]

There have been several studies that have compared prosthetic patch materials in terms of inertness, host tissue response, and adhesion formation. Elliot and Juler[32] studied the inflammatory reaction and fibroblastic ingrowth into polypropylene and expanded PTFE implanted into the abdominal walls of rabbits. They reported only a minimal inflammatory reaction engendered by the expanded PTFE. In contrast, the polypropylene mesh elicited a marked inflammatory reaction and was encased in a mass of dense scar tissue whose contracture had caused distortion of the graft. This same phenomenon was noted in a clinical study in which the outcome was extrusion of the polypropylene mesh.[25] Brown et al.[29] compared the two materials in full-thickness implants in the mid-abdominal wall of guinea pigs. Expanded PTFE produced significantly fewer adhesions than did polypropylene.

The minimal inflammatory reactions elicited by expanded PTFE in these experimental studies were confirmed in our clinical study. No patient exhibited any overt signs of inflammation at the site of the incision, such as erythema, induration, edema, or excessive pain. Moreover, histologic examination of the explants revealed a low foreign body response.

Both the PTFE material and its expanded configuration are critical to its long-term stability and function as a fascial replacement. The physicochemical properties of the polymer have long been known to elicit a negligible tissue reaction within the abdominal cavity.[33] The advent of the technique to expand the material into a microporous sheet of solid nodes connected by fine fibrils rendered it clinically useful. Fibroblasts are able to infiltrate the void spaces of the material and synthesize collagen within the interstices. The PTFE patch is incorporated with minimal inflammation, resulting in a strong, stable repair that exhibits few adhesions.

The clinical course of the wound infections noted in this study underscores the resistance to infection of expanded PTFE. A persistent draining sinus occurred in a patient who had repair of a very large paraileostomy hernia. After several months of antibiotic therapy, this sinus closed and the reconstruction is intact. The other septic complication occurred in a patient where there was massive intra-abdominal contamination from multiple existing intestinal stomas and an intercurrent pelvic abscess. Even though aggressive treatment failed to salvage the reconstruction, the patch material was not extruded from the wound and had to be surgically retrieved. In an animal study comparing bacterial adherence to polypropylene mesh and expanded PTFE, bacterial colonization per square centimeter of polypropylene was 100 times that of expanded PTFE.[29]

The two methods used to repair abdominal wall defects with synthetic prostheses are full-thickness implant or onlay reinforcement. Although both methods are considered safe, the risk of adhesion formation between the bowel and the prosthetic material and the risk of the material eroding into the bowel exists only with full-thickness implants. In this study, full-thickness implants were used in all cases, and no effort was made to reperitonealize beneath the prosthetic patch. During the follow-up period, no complications related to adhesions, erosion, or fistula formation have occurred. There have been several reports where erosion of polypropylene mesh into the esophagus and stomach,[23] the splenic flexure of the colon,[24] and the small bowel[22] have occurred, resulting in obstruction or fistula formation.

The lack of any fistula formation in this study may be fortuitous or may be related to the softness and conformability of expanded PTFE combined with the minimal inflammatory response it elicits. Further study and greater clinical experience should answer this question.

Acknowledgment

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Effects of Indomethacin on Endocrine Responses and Nitrogen Loss after Surgery

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In 14 patients who had elective gastrectomy, 50 mg of indomethacin was administered intrarectally every 6–8 hours after operation until postoperative day 3. Body temperature, plasma cortisol and glucagon concentrations, blood glucose level, urinary catecholamine level, and urinary nitrogen excretion level were compared with those of 16 patients who did not receive indomethacin. Postoperative fever was significantly reduced by indomethacin. Plasma cortisol levels in the indomethacin-treated group were significantly lower on postoperative days 2 and 3. Postoperative increases in plasma glucagon and blood glucose levels were not influenced by indomethacin administration. Urinary epinephrine excretion tended to be inhibited, and urinary norepinephrine excretion was significantly inhibited in the indomethacin-treated group after operation. Urinary nitrogen excretion levels during the observation period were significantly less in the indomethacin-treated group. The cumulative urinary nitrogen level from postoperative days 1–3 in the indomethacin-treated group was 82% of that in the control group. These results indicated that fever reduction by indomethacin after surgery resulted in reduced protein loss, associated with attenuated cortisol and catecholamine responses.

LOSS OF BODY PROTEIN, which is indicated by negative nitrogen balance, is a prominent characteristic of the metabolic changes in patients with infection, trauma, and other stress states. Mechanisms of the protein loss are not well understood, although the involvement of endocrine mediators[1,2] and of neural stimulation[2,3] have been demonstrated. We have previously reported that epidural local anesthetics or epidural morphine reduced nitrogen loss after upper abdominal surgery.[2]

During infection, fever and inflammatory mediators such as prostaglandins are thought to be additional triggering factors of catabolism,[4,5] and it has been suggested that indomethacin, an inhibitor of prostaglandin synthetase, may prevent proteolysis in patients with sepsis.[4]

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In elective clean surgery in which patients have postoperative fever but have no infection, the role of the inflammatory mediators in protein catabolism is not known. It is also not known whether fever *per se* affects the endocrine system and catabolic processes. Therefore, this study was planned to evaluate the effect of fever reduction by indomethacin on endocrine responses and nitrogen balance after elective uncomplicated surgery.

Patients and Methods

Thirty patients who had elective gastrectomy for cancer or ulcers were studied. There were no patients who had hepatic and renal diseases, nor had they any hormonal or metabolic disorders. None had inflammatory diseases or fever, and no patient had any medications before operation. Patients with poor nutritional status, estimated by body weight and plasma albumin level, and patients who received noncurative operation because of advanced cancer were excluded from the study. Patients in whom operative blood loss exceeded 1000 mL were also excluded. Informed consent was obtained for participation in the study.

All of the patients were operated on while under epidural analgesia with the use of 0.5% plain bupivacaine extending to the Th_{3-4} segment. The detailed technique of the epidural analgesia employed was the same as has been previously described.[6] For postoperative pain relief, morphine hydrochloride 3 mg/10 mL saline was administered through the epidural catheter every 8 hours, starting at 1 hour after operation until 6:00 A.M. on postoperative day 4. By this regimen, patients were all pain-free after operation and did not require supplementary analgesics.

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TABLE 1. *Patient Characteristics*

	Control Group (N = 16)	Indomethacin-treated Group (N = 14)
Sex: male/female	13/3	10/4
Disease: cancer/ulcer	15/1	12/2
Gastrectomy: total/ partial	7/9	1/13
Age (years)	61 ± 3	60 ± 3
Height (cm)	157.1 ± 1.4	158.4 ± 2.2
Weight (kg)	50.7 ± 1.5	53.7 ± 2.2
Albumin (g/dL)	4.2 ± 0.1	3.8 ± 0.1
Operation time (min)	212 ± 12	199 ± 11
Blood loss (mL)	426 ± 62	383 ± 58

Intravenous infusion during operation was restricted to lactated Ringer's solution only. However, when blood loss during operation exceeded 500 mL, the same amount of citrated whole blood was transfused. After operation, 1000 mL of 10% glucose solution was administered. On the first 3 postoperative days, 3 g/kg body weight of glucose was infused, together with appropriate amounts of electrolyte solutions, the total amount of water being adjusted to 2000–2500 mL. No amino acid solution was infused throughout the study. Food intake did not start before postoperative day 4. All of the operations started between 9:00 A.M. and 10:00 A.M., after overnight fasting.

The patients were randomly allocated into two groups: the indomethacin-treated group (N = 14) and the control group (N = 16). In the indomethacin-treated group, the suppository containing indomethacin 50 mg was administered starting at 1 hour after operation, every 6 hours on the day of operation, and every 8 hours on the first 3 postoperative days. No indomethacin was administered to the control group.

Peripheral arterial and venous blood samples were drawn five times from each patient: before preanesthetic medication, 30 minutes after skin closure, and at 8:00 A.M. on postoperative days 1, 2, and 3. A part of each venous blood sample was transferred to a chilled tube, and the plasma for cortisol analysis was immediately separated. Another part of the sample was transferred to a chilled tube containing EDTA-2K2Na/Trasylol® (Aprotinin, Bayer AG, Leverkusen, West Germany) and the plasma for the measurement of glucagon was immediately separated. Each plasma sample was stored frozen until analysis. Glucose levels were measured in the arterial blood samples. Twenty-four–hour urine samples were collected in glass bottles containing 15 mL of 6 N HCl from the day before operation until postoperative day 3. Plasma cortisol levels were measured by radioimmunoassay with the use of the GammaCort cortisol kit (Baxter Travenol Diagnostics, Inc., Cambridge, MA), glucagon levels by radioimmunoassay with the use of pancreatic glucagon-specific antibody,[7] and glucose levels by a routine glucose oxidase method. Measurement of urinary epinephrine and norepinephrine levels was performed by use of a high-speed ion-exchange column chromatography and the automated trihydroxyindol method.[8] Urinary nitrogen was measured by the micro-Kjeldahl method.

Values were expressed as mean ± standard error of the mean. Statistical analysis was performed with the use of Wilcoxon's rank sum test; $p < 0.05$ was considered significant.

Results

The characteristics of the patients studied are summarized in Table 1. The ratio of total gastrectomy in the control group tended to be greater than in the indomethacin-treated group. However, the other characteristics were all comparable between the groups.

TABLE 2. *Axillary Temperature (C)*

	Postoperative Days							
	−1	0	1		2		3	
Group	A.M.	P.M.	A.M.	P.M.	A.M.	P.M.	A.M.	P.M.
Control group								
N	16	16	16	16	16	16	16	16
Mean	36.2	37.9	37.4	37.7	37.2	37.3	36.9	37.4
SEM	0.1	0.3	0.1	0.1	0.1	0.2	0.1	0.2
Indomethacin-treated group								
N	14	14	14	14	14	14	14	14
Mean	36.3	37.4	37.2	37.1	36.8	36.8	36.5	36.8
SEM	0.1	0.2	0.2	0.1	0.1	0.1	0.1	0.1
p	NS	NS	NS	<0.01	<0.01	<0.05	<0.01	<0.01

Day −1 and day 0 indicate the day before operation and the day of operation, respectively.

SEM = standard error of the mean; NS = not significant.

TABLE 3. *Plasma Cortisol Concentrations (nmol/L)*

Group	Before Premedication	30 Minutes after Operation	Postoperative Days 1	2	3
Control group					
N	16	16	16	16	16
Mean	317	698*	359	384†	408†
SEM	22	43	28	28	41
Indomethacin-treated group					
N	14	14	14	14	14
Mean	265	679*	364	287	262
SEM	15	25	50	12	13
p	NS	NS	NS	<0.01	<0.01

* $p < 0.01$ (*vs.* before premedication).
† $p < 0.05$ (*vs.* before premedication).

SEM = standard error of the mean; NS = not significant.

Body Temperature

Axillary temperature was recorded at 6:00 A.M., 10:00 A.M., 3:00 P.M., 6:00 P.M., and 9:00 P.M. in each patient. Individual maximum values in the morning and/or those in the afternoon were averaged and listed in Table 2. In the control group, highest body temperature was observed in the afternoon on the day of operation, after which body temperature gradually returned toward normal. In the indomethacin-treated group, body temperature also showed a peak value in the afternoon on the day of operation, although the value tended to be lower than in the control group. On the first 3 postoperative days, mean values of body temperature in the indomethacin-treated group were consistently lower than in the control group and showed statistically significant differences ($p < 0.05$ or $p < 0.01$, Table 2).

Cortisol

The preoperative cortisol level in the control group was higher than in the indomethacin-treated group, but the difference was not statistically significant. In the control group, plasma cortisol concentration increased at 30 minutes after operation and lowered thereafter. In the indomethacin-treated group, plasma cortisol concentrations were almost the same as in the control group at 30 minutes after operation and on postoperative day 1. However, plasma cortisol concentrations on postoperative days 2 and 3 were significantly lower ($p < 0.01$) in the indomethacin-treated group than in the control group (Table 3).

Glucagon

The preoperative plasma glucagon concentration in the control group was slightly lower than in the indomethacin-treated group, although there was no significant difference between the groups. In the control group, plasma glucagon concentration did not change from the baseline value at 30 minutes after operation. On postoperative day 1, glucagon concentration in the control group increased to 160% of the baseline value and then gradually decreased. Plasma glucagon levels in

TABLE 4. *Plasma Glucagon Concentrations (pmol/L)*

Group	Before Premedication	30 Minutes after Operation	Postoperative Days 1	2	3
Control group					
N	15	15	15	15	15
Mean	21.2	19.8	34.2*	33.9*	27.6†
SEM	4.6	1.6	3.5	3.3	2.4
Indomethacin-treated group					
N	13	13	13	13	12
Mean	24.4	25.3	38.7*	35.3*	29.3*
SEM	1.6	2.0	5.0	3.2	2.2
p	NS	<0.05	NS	NS	NS

* $p < 0.01$ (*vs.* before premedication).
† $p < 0.05$ (*vs.* before premedication).

SEM = standard error of the mean; NS = not significant.

TABLE 5. *Blood Glucose Concentrations (mmol/L)*

Group	Before Premedication	30 Minutes after Operation	Postoperative Days 1	2	3
Control group					
N	16	16	15	16	16
Mean	4.76	7.95*	5.66*	5.04	5.66*
SEM	0.14	0.69	0.25	0.20	0.25
Indomethacin-treated group					
N	14	14	14	13	14
Mean	4.82	7.06*	5.88*	4.98	5.10
SEM	0.13	0.37	0.25	0.23	0.19
p	NS	NS	NS	NS	NS

* $p < 0.01$ (*vs.* before premedication).

SEM = standard error of the mean; NS = not significant.

the indomethacin-treated group showed a similar pattern as in the control group. However, values in the indomethacin-treated group were consistently higher than in the control group. There was a significant difference ($p < 0.05$) between the groups at 30 minutes after operation (Table 4). When percentage changes from the baseline values were compared, there were no significant differences between the groups at any points in time after operation.

Glucose

In the control group, blood glucose levels increased at 30 minutes after operation and returned toward the preoperative level thereafter. Blood glucose levels in the indomethacin-treated group showed an almost similar pattern as in the control group. There were no significant differences in blood glucose values between the groups (Table 5).

Urinary Epinephrine Excretion

In the control group, the urinary epinephrine level showed an approximately threefold increase on the day of operation, then gradually returned toward the preoperative value. Urinary epinephrine excretion on postoperative day 3 was still greater than the preoperative value. In the indomethacin-treated group, urinary epinephrine increased on the day of operation, remained high on postoperative day 1, and returned toward the preoperative value thereafter. Urinary epinephrine excretion on the day of operation and on postoperative days was consistently less than that of the control group, although the differences were not significant (Table 6).

Urinary Norepinephrine Excretion

In the control group, urinary norepinephrine increased only slightly on the day of operation but then increased to higher levels on the postoperative days, showing a maximum value on postoperative day 1. In the indomethacin-treated group, the time course of urinary norepinephrine excretion was the same as in the control group. However, norepinephrine excretion in the indomethacin-treated group was significantly less ($p < 0.01$) than in the control group on postoperative days 2 and 3 (Table 7).

Urinary Nitrogen Excretion

In the control group, sustained nitrogen excretion levels of more than 140 mg/kg/day were observed on postoperative days. In the indomethacin-treated group, the urinary nitrogen excretion level on the day of operation was significantly less ($p < 0.05$) than in the control group. Nitrogen excretion levels on postoperative days were consistently less in the indomethacin-treated group than in the control group. There were significant differences ($p < 0.05$) in nitrogen excretion levels on postop-

TABLE 6. *Urinary Epinephrine Excretion (mmol/day)*

Group	Postoperative Days −1	0	1	2	3
Control group					
N	16	16	16	16	16
Mean	34	111*	82*	61†	58†
SEM	6	23	14	13	15
Indomethacin-treated group					
N	13	14	14	14	14
Mean	33	68*	67†	43	47
SEM	5	12	10	7	10
p	NS	NS	NS	NS	NS

* $p < 0.01$ (*vs.* day −1).

† $p < 0.05$ (*vs.* day −1).

Day −1 and day 0 indicate the day before operation and the day of operation, respectively.

SEM = standard error of the mean; NS = not significant.

TABLE 7. *Urinary Norepinephrine Excretion (mmol/day)*

Group	Postoperative Days −1	0	1	2	3
Control group					
N	16	16	16	16	16
Mean	294	341	503*	467†	417*
SEM	66	43	44	45	45
Indomethacin-treated group					
N	13	14	14	14	14
Mean	270	354	408	307	226
SEM	47	63	61	50	36
p	NS	NS	NS	<0.01	<0.01

* $p < 0.01$ (*vs.* day −1).

† $p < 0.05$ (*vs.* day −1).

Day −1 and day 0 indicate the day before operation and the day of operation, respectively.

SEM = standard error of the mean; NS = not significant.

erative days 1 and 3 between the groups. Cumulative nitrogen excretion of the 3 postoperative days was 82% of that of the control group, the difference being statistically significant ($p < 0.05$, Table 8).

Postoperative Course

No side effects related to the administration of indomethacin were noted. All patients recovered uneventfully.

Discussion

In this study, indomethacin administered for 4 days after elective gastrectomy reduced postoperative fever associated with decreased cortisol and catecholamine responses and reduced nitrogen loss. Aspirin-like drugs are known to reduce fever resulting from infection or pyrogen mediated by the inhibition of synthesis of prostaglandins in the central nervous system.[9] Although the mechanism of postoperative fever is not clear, our present results indicate that febrile response to clean elective surgery can also be effectively reduced by indomethacin.

On postoperative days 2 and 3, when fever was significantly reduced by indomethacin, both cortisol and norepinephrine responses were inhibited. Indomethacin has an analgesic effect, and postoperative pain is considered to stimulate adrenocortical and sympathetic responses.[2,10] It is unlikely, however, that the lowered hormonal responses in the indomethacin-treated group resulted from the analgesic effect of the drug because postoperative pain was almost completely relieved by epidural morphine, irrespective of the indomethacin treatment.

The mechanism of the reduced cortisol and catecholamine responses by indomethacin is unclear. There are many studies as to whether prostaglandins mediate adrenal steroidogenesis, but the results are controversial.[11-14] Although prostaglandins have been reported to modulate sympathetic nerve transmission, the suppressive or

TABLE 8. *Urinary Nitrogen Excretion (mg/kg)*

Group	Postoperative Days −1	0	1	2	3	Cumulative Amount (Days 1–3)
Control group						
N	14	16	16	16	16	16
Mean	96	152	146	141	143	430
SEM	12	11	11	9	13	29
Indomethacin-treated group						
N	11	14	14	14	14	14
Mean	96	112	117	133	104	354
SEM	17	17	12	16	9	33
p	NS	<0.05	<0.05	NS	<0.05	<0.05

Day −1 and day 0 indicate the day before operation and the day of operation, respectively.

SEM = standard error of the mean; NS = not significant.

facilitating effect depends on the types of prostaglandins.[15] Reports on the effects of prostaglandins on the release of catecholamines from the adrenal gland are conflicting, probably because of the difference in species studied and the types of prostaglandins.[16–18] It is thus difficult to explain the hormonal suppression by the inhibition of prostaglandin synthesis in the peripheral organs. Weeke and Gundersen[19] and Kim et al.[20] reported that artificial hyperthermia induced by heating elicited an increase in plasma norepinephrine. This fact is in accordance with our result in which norepinephrine response was decreased by fever reduction. Change in body temperature may also have an influence on activity in the pituitary adrenocortical axis, although no reported evidence is available.

Glucagon, together with cortisol and catecholamines, is an important catabolic hormone.[21,22] We have suggested that glucagon may contribute to postoperative nitrogen loss.[2] In contrast to the suppressive effect of indomethacin on cortisol and catecholamine responses, this drug did not affect postoperative glucagon response. Glucagon is thus not responsible for the decreased nitrogen loss in this study.

We have reported the inhibitory effect of epidural blockade and splanchnic nerve blockade on hyperglycemic response as well as endocrine responses.[23] However, hyperglycemic response to gastrectomy was mainly observed during and immediately after operation, and neither type of neural blockade affected the slightly elevated blood glucose levels in the later postoperative period.[23] In this study, indomethacin administered after surgery also had no influence on blood glucose levels, although it suppressed febrile and hormonal responses, as mentioned above.

Postoperative administration of indomethacin not only suppressed the endocrine responses but also reduced nitrogen loss. Rowe et al.[24] reported that indomethacin given after fracture stress in rats suppressed the increase in fibrinogen, an acute phase reactant, which may suggest a reduced catabolic response to trauma. They also studied the effects of indomethacin combined with prostaglandin E_2 on the urinary excretion of nitrogen, urea, and creatinine and found that the production of the nitrogenous compounds was reduced by indomethacin.[25] Goldberg et al.[26] reported that administration of indomethacin *in vivo* to endotoxin-treated rats prevented the increase in proteolysis in isolated muscle tissue. These results suggest that inhibition of prostaglandins by indomethacin results in a reduced protein degradation. However, the involvement of the prostaglandin system in protein loss after surgery is not proven.

Because catabolic hormones are important mediators in protein catabolism,[1,2] the attenuated hormonal responses caused by indomethacin possibly contributed to the decreased nitrogen loss in this study. On the other hand, Baracos et al.[4] reported that rat muscle incubated in a medium at 39 C showed a greater increase in proteolysis than at normal body temperature. This result suggests that an increase in body temperature directly promotes protein breakdown in the muscle, and therefore fever reduction by indomethacin may have resulted in the reduced negative nitrogen balance.

In this study, fever reduction after surgery did not cause any detrimental effect. A benefit in using prostaglandin synthetase inhibitors in endotoxin or septic shock has been demonstrated,[27] although caution in its use has been suggested.[28] Whether the reduction of postoperative fever benefits patients should further be investigated.

In conclusion, the administration of indomethacin after elective gastrectomy resulted in reduced negative nitrogen balance after surgery. This reduced catabolic response may have been caused by associated inhibition of cortisol and catecholamines and by the direct effect of fever reduction.

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The Role of Percutaneous Angioplasty in the Management of Chronic Hemodialysis Fistulas

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One hundred forty-one dilatations of stenotic lesions in dialysis access fistulas were performed. The initial success rate was 82%. The one-year patency rate was 45%, with a 2-year patency rate of 24%. Best results were obtained with a discrete stenosis at a graft-to-vein anastomosis. The procedure can be done on an outpatient basis and, although long-term results are poor, in appropriate patients multiple dilatations can be performed to keep a fistula functioning for many years.

THE INCREASING NUMBER of patients with end-stage renal disease in the United States has created the need for reliable vascular access. The initial and favored procedure for the creation of an access fistula is the direct arteriovenous (A-V) fistula of the Brescia-Cimino type.[1,2] If this fistula fails or is not feasible, a graft made of polytetrafluoroethylene (PTFE) or bovine carotid artery can be placed subcutaneously between an artery and vein to provide access.[3–6]

The most common problems encountered with A-V fistulas and grafts are inadequate dialysis and graft thrombosis.[2,7] These usually result from a venous outflow stenosis or, less frequently, from inadequate inflow from an arterial lesion. Treatment has consisted of surgical revision of the stenosis or graft replacement at a different site. An alternative to surgical revision is treatment *via* percutaneous angioplasty. In this article we present our experience with dilatation of 141 stenotic lesions in dialysis access fistulas over a 7-year period.

Materials and Methods

Over the past 7 years we have performed 141 dilatations in 95 patients. Indications for angiography included repeated graft thrombosis (31 patients), inadequate dialysis with high recirculation (65 patients), high venous pressure during dialysis (75 patients), arm edema (15 patients), and enlarging venous aneurysms or graft pseudoaneurysms (13 patients).

One hundred twelve dilatations were performed in patients with grafts. Of these, three stenoses were at the arterial anastomosis, and 93 at the venous anastomosis. Sixteen venous stenoses were proximal to the anastomosis in the axillary or subclavian vein. Twenty-nine lesions were dilated in patients with direct A-V fistulas. Of these, 15 were in the outflow vein within 5–6 cm of the A-V connection and 14 in a vein distant from the A-V connections (five at the elbow, five in the axillary vein, and four in the subclavian vein).

Direct A-V fistulas were studied either by direct brachial artery puncture or by a venous puncture with inflation of a pressure cuff proximally to allow reflux of contrast into the arterial system.[8,9] Grafts were studied *via* a 5-F catheter placed directly in the venous end of the graft. If the arterial anastomosis needed to be visualized, a pressure cuff was inflated proximally to allow reflux of contrast into the arterial system. No study results were considered negative until the entire venous system to the level of the subclavian vein was visualized. Spurious narrowing of the axillary vein may be created by compression of chest wall muscles when the arm is in an adducted position, so this area is always studied with the arm abducted.

After delineation of the lesion, the stenosis was crossed with a 5-F catheter and a pressure pullback obtained. An appropriate size dilatation catheter was then chosen, depending on the size of the graft and normal vein on either side of the stenosis. Lesions longer than 4 cm were referred for surgery because these were univer-

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TABLE 1. *Patency Rates of Percutaneous Angioplasty*

Site	Initial	6 Months	1 Year	2 Years	3 Years	5 Years
Arterial anastomotic stenosis	2/3 (67%)	2/2 (100%)	1/2 (50%)	0/2	0/2	0/2
Direct arteriovenous fistula Anastomotic venostenosis	9/15 (60%)	4/9 (44%)	3/8 (38%)	1/7 (14%)	0/7	0/4
Graft anastomotic venostenosis	80/93 (86%)	42/71 (59%)	32/64 (50%)	16/50 (32%)	6/38 (16%)	0/20 (0%)
Far proximal venous stenosis (graft and direct arteriovenous fistula)	25/30 (83%)	13/25 (52%)	8/23 (35%)	2/20 (10%)	1/18 (6%)	0/14
Total	116/141 (82%)	61/107 (57%)	44/98 (45%)	19/79 (24%)	7/63 (11%)	0/40 (0%)

sally unsuccessful in our early experience. The dilatation catheter was introduced through the graft. There have been no problems introducing large balloon catheters through grafts that are older than 1 month old, and no pseudoaneurysms have developed at the puncture site after dilatation. Before dilatation the patient is given 3000 units of heparin intravenously (I.V.). Dilatation of veins may be painful. Infiltration of lidocaine around the stenotic lesion before balloon inflation may alleviate some of the pain. The first 50 cases were dilated with standard balloons that generated pressure of 3–4 atmospheres. The last 91 dilatations were done with high-pressure balloons that generate 10 atmospheres pressure. The dilatation pressure is monitored and the balloon left inflated for 1–2 minutes. Most patients received treatment on an outpatient basis and were observed for 30 minutes in the angiography suite after the procedure before being sent home.

Immediate results after the procedure were evaluated by angiography and pressure pullback. Long-term results were evaluated *via* clinical symptoms and efficacy of dialysis.

Results

Three patients died within 2 months of the procedure (causes of death unrelated to the dilatation), and 18 patients were lost to follow-up. Initial and long-term results are summarized in Table 1.

There were nine complications (6%): six graft thromboses within 48 hours of the procedure and three venous ruptures. All three ruptured veins were controlled by manual occlusion of the fistula and pressure dressings. None required transfusion or emergency surgery. All three were operated on electively within 1–7 days after procedure.

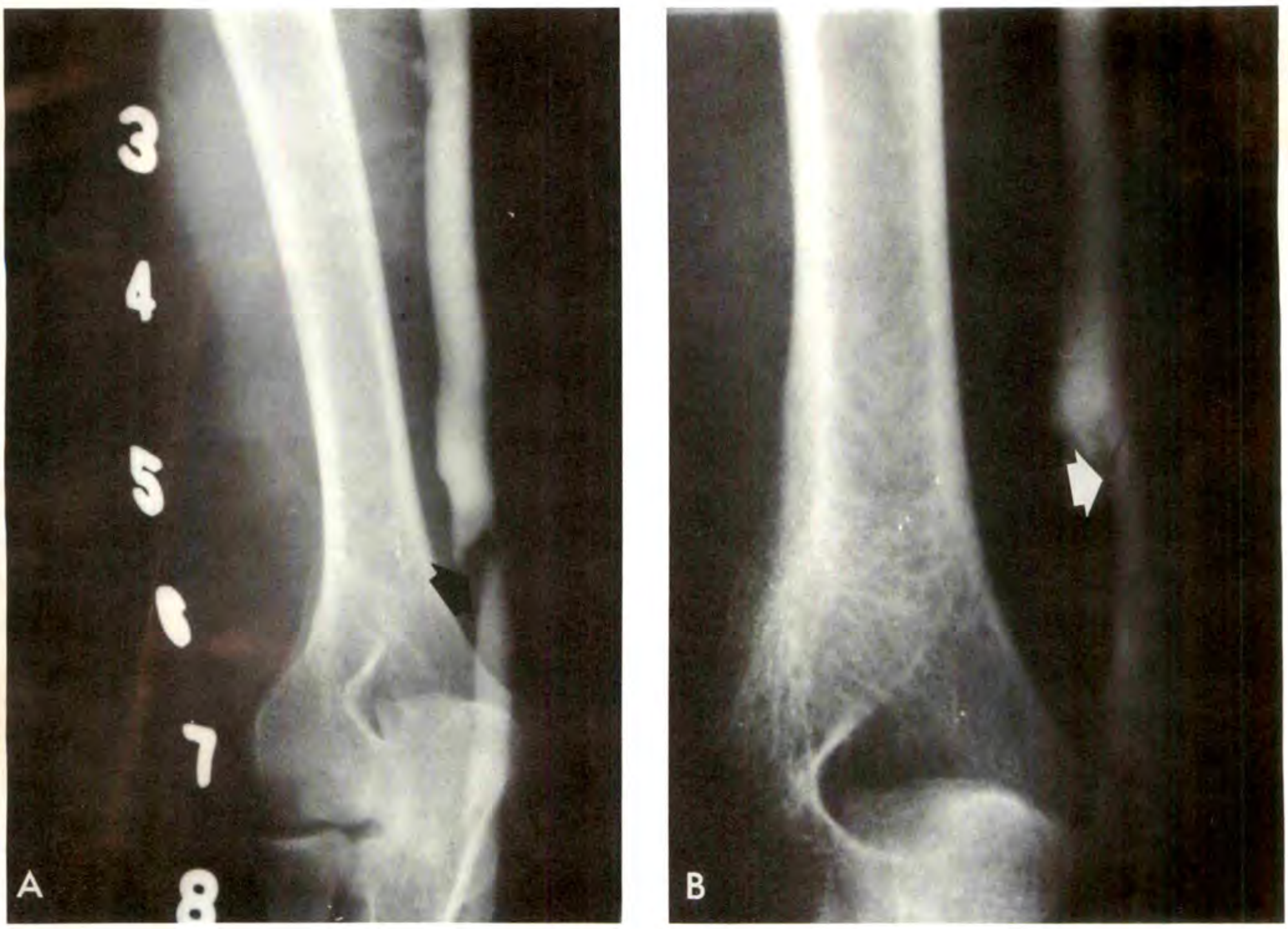
Discussion

Clinical problems necessitating fistula study include repeated thrombosis and inadequate dialysis as manifested by arterial sucking, high venous pressure, and recirculation of dialyzed blood.[2,9] These problems usually indicate poor arterial inflow or inadequate venous outflow. Other problems include arm edema, enlarging venous or graft aneurysms and pseudoaneurysms, and venous varicosities. These usually result from venous outflow obstruction.

Over the past 2 years, 800 graft and direct A-V fistulas have been surgically revised at Downstate Medical Center. Causes of fistula failure included a venous outflow stenosis in 70%, an arterial stenosis in 10%, and a combination of the two in 15%. Both the venous and arterial lesions invariably resulted from intimal hyperplasia, even in those fistulas corrected as early as 2 months after creation.

The most common operation performed was a thrombectomy and venous patch angioplasty. Only 20% of patients with a vascular access problem have diagnostic angiography. The remainder generally have complete fistula thrombosis and have surgical correction. Of those patients studied angiographically, approximately 90% have a venous outflow problem, either a total occlusion or significant stenosis. Approximately 40% of all patients studied have a lesion amenable to angioplasty.

Venous stenoses in direct A-V fistulas generally occur within 5–6 cm of the A-V communication. Graft venous stenoses usually occur at the graft-to-vein anastomosis or within 2–3 cm of the anastomosis.[9–13] Anastomotic venous lesions result from the combination of intimal hyperplasia and perivenous fibrosis. These stenoses are often resistant to dilatation and necessitate the use of high-pressure balloons.[14] Our last 91 angioplasties have been performed with high-pressure catheters (10 atmospheres), resulting in improved initial results (88% *vs.* 67% with standard balloons generating 3–5 atmospheres). Long-term results have been the same with both types of balloons. The turbulence and abnormal shear stresses thought to play a role in the deposition of platelets and thrombi that eventually lead to endovenous fibrosis and stricture are still present after dilatation and inevitably lead to restricture.

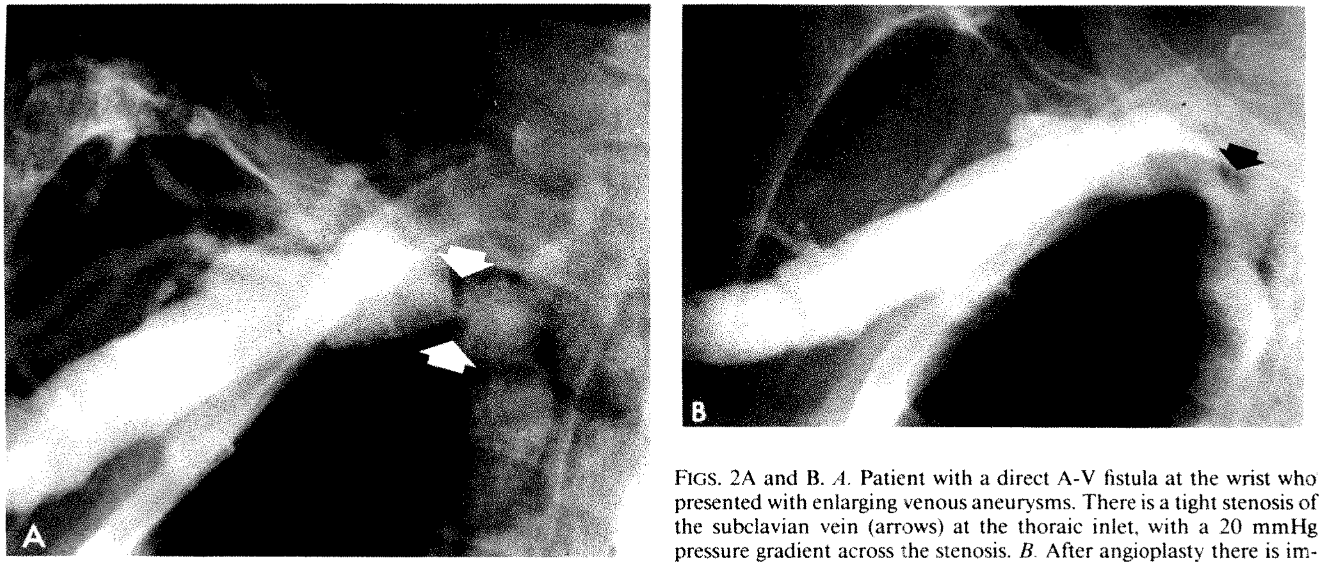


FIGS. 1A and B. *A*. There is a tight stenosis (arrow) at the anastomosis of a GORE-TEX (W. L. Gore and Associates, Inc.) graft to the basilic vein. *B*. After angioplasty there is significant widening of the stenosis (arrow), and the pressure gradient has been reduced from 60 mmHg to 0 mmHg.

Venous stenoses near the anastomosis of a direct A-V fistula are generally longer than the more discrete graft anastomotic venous lesions. This probably accounted for the better results obtained with graft dilatations (Fig. 1). Our results with long stenoses were so poor that we no longer perform dilatation in patients with lesions longer than 4 cm. Two total occlusions were treated. One was a short segment occlusion at the anastomosis of a graft to the basillic vein and the other was at the anastomosis of a graft to the axillary vein. A straight wire passed through the occluded segment easily. One dilatation was unsuccessful, and the other was patent for only 2 weeks. We now refer patients with total occlusions for surgical correction. New anastomotic sites are not dilated for a minimum of 4 weeks after operation, to preclude dehiscence of the anastomosis.

Stenosis may also occur within a graft because of progressive pseudointimal hyperplasia or trauma from repeated puncture. We have not dilated intragraft lesions because of the lack of muscular structure and elasticity in a graft and the subsequent risk of graft rupture. Intragraft lesions are usually long because of the widespread nature of pseudointimal hyperplasia.

Thirty proximal venous strictures were dilated. These tend to occur at sites of physiologic narrowing, the most common being in the cephalic vein at the elbow; the axillary vein, which is compressed by chest wall muscles when the arm is adducted; and the subclavian vein as it crosses between the clavicle and first rib (Fig. 2). Hypertrophied valves may also cause venous obstruction. Large valves most commonly occur in the axillary vein at the lower border of the subscapularis muscle and in the subclavian vein 2–3 cm proximal to its junction with the internal jugular vein (Fig. 3). Sites of previous central venous lines may also stricture when subjected to abnormal flow patterns. Three of the subclavian vein stenoses were at sites of a previous Shiley catheter. The turbulence created by high flow in a venous system with a physiologic or iatrogenic narrowing leads to eventual intimal hyperplasia and stenosis. Because of the fre-



FIGS. 2A and B. *A*. Patient with a direct A-V fistula at the wrist who presented with enlarging venous aneurysms. There is a tight stenosis of the subclavian vein (arrows) at the thoracic inlet, with a 20 mmHg pressure gradient across the stenosis. *B*. After angioplasty there is improvement of the lesion (arrow), with a decrease in the pressure gradient to 3 mmHg. There is still a residual narrowing caused by compression of the vein as it passes between the clavicle and first rib.

quency of proximal venous lesions (21%), all patients should be evaluated to the level of the subclavian vein before study results are considered negative. If angiograms are equivocal, pressure pullback from the superior vena cava to the anastomosis should be performed. Although there is normally a gradual venous pressure increase as one pulls back from the superior vena cava to the axillary vein, a discrete gradient of more than 5–10 mmHg should be considered significant. Because the anatomic problem that precipitated these stenoses is still present after dilatation, proximal venous lesions tend to recur more quickly than anastomotic stenoses.

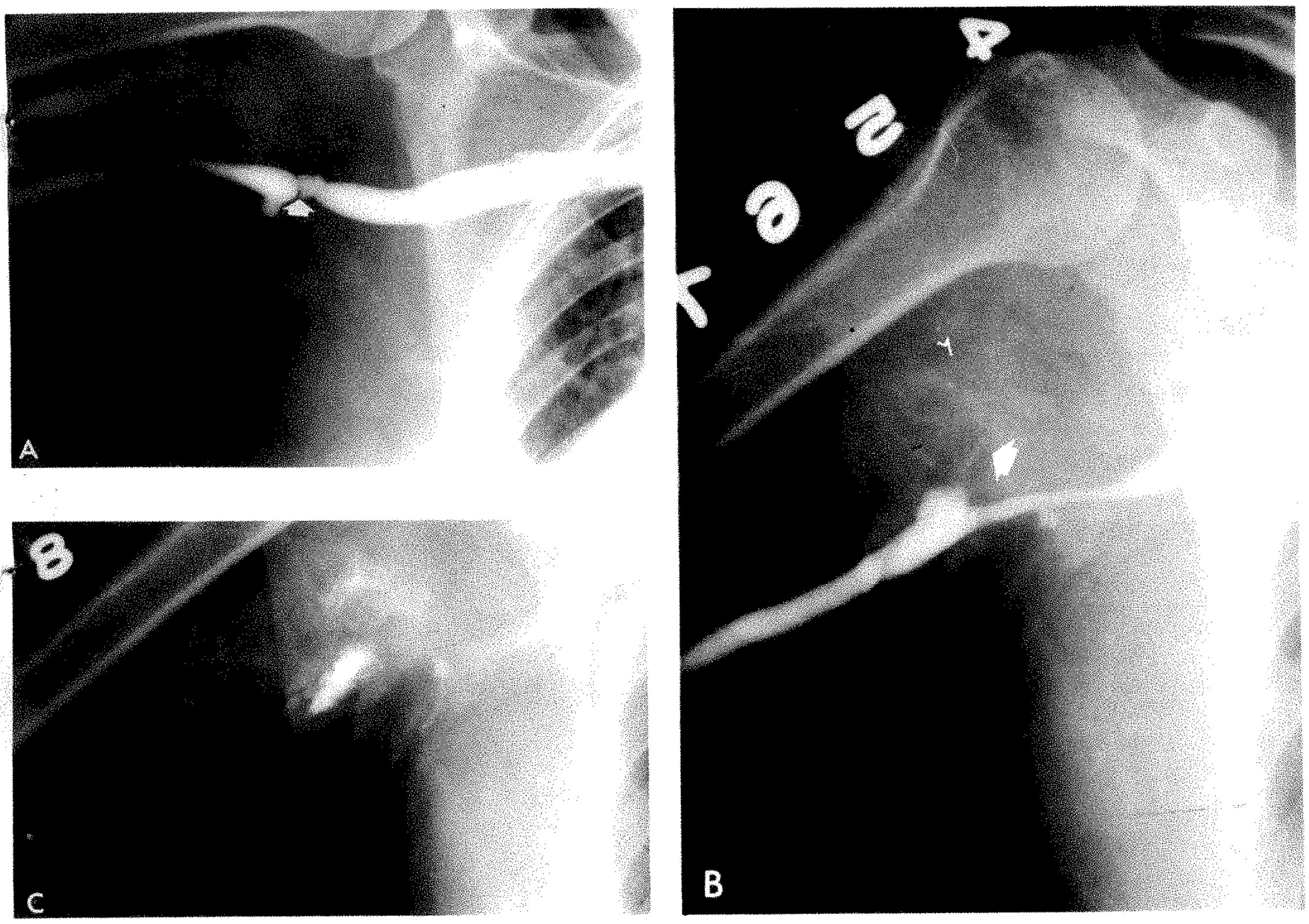
Venous stenosis and hypertension may cause other problems such as arm edema, enlarging venous aneurysms and varicosities, and enlarging graft pseudoaneurysm.[9,15] These clinical problems should alert the physician to a possible venous outflow obstruction and study should include the entire venous system to the subclavian vein. These problems can often be alleviated by angioplasty (Fig. 2).

Most angioplasties were technically not difficult and were performed on an outpatient basis. Once a graft has been incorporated into the subcutaneous tissues, puncture of the graft and introduction of a balloon catheter can be performed without difficulty. No significant problems have been encountered in removal of the catheter from the graft, and no pseudoaneurysms have occurred at the puncture site.

Complications included graft thrombosis (4%) and extravasation at the dilatation site (2%) (Fig. 3). Extravasation was controlled by compression of the fistula and a pressure dressing at the site of venous rupture. No patients required emergency surgery or blood transfusion.

It is clear that angioplasty, although initially effective, does not solve the long-term problem of recurrent venous outflow obstruction. However, angioplasty is safe and relatively simple and can be performed on an outpatient basis. A failed angioplasty or fistula thrombosis means the patient can still have the surgical correction that would have been done before angioplasty. Dilatation can be repeated numerous times to keep a fistula functioning for many years, often for the rest of the patient's life. Several patients have had multiple dilatations to keep a fistula patent for 4–5 years. We feel that any patient with a stenotic lesion less than 4 cm in length at or near a graft-to-vein anastomosis should have angioplasty before surgical repair. Expected patency rates at this location are 50% at 1 year and 32% at 2 years. Patients with proximal lesions in the axillary or subclavian vein, areas difficult to approach surgically, should also be treated primarily with angioplasty. Patients with a Brescia-Cimino type direct A-V fistula at the wrist who have a good radial artery and cephalic vein proximal to the stenosis may do better with a more proximal side-to-side direct fistula because of the high long-term patency of this type of vascular access.

Patients on chronic hemodialysis for more than several years are likely to have multiple surgical corrections of their vascular access. More aggressive angiography at the earliest sign of any problem coupled with angioplasty can help preserve many of these fistulas and decrease the hospitalization time and the number of corrections in this group of patients who have already had



FIGS. 3A–C. *A*. Patient with a GORE-TEX graft to basilic vein anastomosis who presented with high venous pressure during dialysis. There is a stenosis in the axillary vein caused by a hypertrophied valve (arrow). *B*. After angioplasty there is still narrowing of the axillary vein and the beginning of extravasation (arrow). *C*. A late film demonstrates contrast extravasation. The patient was treated by compression of the graft and a pressure dressing. The fistula was electively corrected.

and are still likely to have numerous surgical procedures during their lives.

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Total Thyroidectomy

The Preferred Option for Multinodular Goiter

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Total thyroidectomy is an operation that has generally been reserved for the management of differentiated thyroid carcinoma. Over the last decade total thyroidectomy has become used increasingly and is now the preferred option in the authors' unit for the management of multinodular goiter affecting the entire gland. Over the period from 1975 to 1985, 853 thyroidectomies have been performed for multinodular goiter; of these, 115 have been total thyroidectomies. During that time, the incidence of total thyroidectomy for multinodular goiter has increased in percentage terms from 9% in 1975 to 50% in 1985. There have been two cases of permanent hypoparathyroidism and one case of permanent recurrent laryngeal nerve injury, and these occurred in patients who had less than total thyroidectomy. Total thyroidectomy is an appropriate operation for the management of diffuse multinodular goiter where the entire gland is involved because it precludes patients from requiring further surgery for recurrent disease, with its high associated risks. It must be emphasized, however, that protection of the recurrent laryngeal nerve and parathyroid glands must still be paramount in dealing with benign thyroid disease.

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IN MANY AREAS OF SURGERY there is a balance between the benefits from extensive resection in terms of palliation and cure and the increased potential for complications associated with more radical procedures. Total thyroidectomy is such a procedure, where considerable controversy still exists with respect to its use for conditions such as differentiated thyroid carcinoma.[1,2] Even more controversial is its use for benign thyroid disease such as multinodular goiter or thyrotoxicosis.[3] On the other hand, re-operation for recurrent disease carries a very significant risk of damage to both the recurrent laryngeal nerves and the parathyroid glands.

Although total thyroidectomy has always been an option for the management of multinodular goiter, this approach was pursued in 1983, after the introduction of a revised technique for total thyroid lobectomy in which dissection is performed, hugging the true capsule of the gland.[4] By 1985, the policy of the Department of Surgery, the University of Sydney at Royal North Shore Hospital, had been established such that total thyroidectomy had become the preferred option for multinodular goiter when the whole gland was involved, with no visible or palpable normal thyroid tissue, and where it was considered that the operation could be performed without risk of complications. The aim of this article is to review the experience of our department with total thyroidectomy for multinodular goiter and to make an assessment on the justification of the approach taken toward total thyroidectomy for multinodular goiter.

Patients and Methods

During the period from 1975 to 1985, 2052 thyroidectomies were performed in the University of Sydney Department of Surgery at Royal North Shore Hospital. There were 853 procedures carried out for multinodular goiter during this period and, of these, 115 were total thyroidectomies. During this same period, 104 secondary thyroidectomies were carried out for recurrent multinodular goiter causing compression or for intrathoracic goiter. Many of these patients had had their original surgery (usually a bilateral subtotal thyroidectomy) performed in our department 15–20 years previously. All information relating to these operative procedures,

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and to their pathologic conditions and complications, was recorded prospectively and stored in the Department of Surgery Thyroid Data Base. This data base, stored on a DEC PDP-11/73 computer, now contains detailed information on 6024 thyroidectomies performed over the last 25 years.

Preoperative investigations, including thyroid function tests and routine biochemistry, were performed on all patients. Other tests, such as nuclear and ultrasonographic scanning and fine-needle aspiration biopsy, were performed selectively. Vocal cord function was assessed routinely before and after operation by an independent otolaryngologist, as well as by the anesthetist at the time of extubation.[5] Stasis-free serum calcium levels were also measured both before operation and on day 1 and day 5 after operation.

Operative Technique

Within our department thyroidectomy is performed by use of a standard operative technique[6,7] while patients are under general anesthesia, with muscle relaxation and intubation. With the neck extended, the skin is marked and infiltrated with POR-8, flaps are raised, and the strap muscles are divided transversely. Attention is first turned to one lobe where the upper pole is mobilized through the avascular space with individual ligation of the vessels to protect the external laryngeal nerve, according to our long-standing technique. The lower pole is then mobilized by ligating individual tertiary branches of the veins and arteries on the thyroid capsule, with gradual dissection of the vasculature from the gland by ligation and division of the perforating vessels at the capsule and preservation the blood supply of the parathyroid glands (Fig. 1). These glands may often be preserved on a slender pedicle of artery and vein. Any parathyroid gland that cannot be salvaged because of its anatomic location is minced and placed in the sternomastoid muscle.

Before 1983, the recurrent laryngeal nerve was routinely identified during dissection,[5,7] but, since that time, the nerve is protected by the technique of capsular dissection. As emphasized by Harness et al.,[8] the nerve is not sought laterally early in the procedure, but as dissection proceeds to the area of the ligament of Berry the nerve will often be encountered as it courses through or close to the ligament itself.

The remaining lobe is removed by the same technique. Where there is considered to be significant risk to the nerve, especially as it enters the cricothyroid muscle, a small remnant of thyroid tissue may be retained if necessary to preserve the integrity of the nerve. Hemostasis is secured, the strap muscles and platysma layer sutured, and the skin closed with subcuticular sutures without drainage. It is important to emphasize, as does Perzik,[3] that the parathyroid glands and recurrent laryngeal nerve are not routinely sought. Rather, the main object is to avoid them by the capsular technique but to be ready and able to recognize and preserve them if they appear in the operative field during dissection.

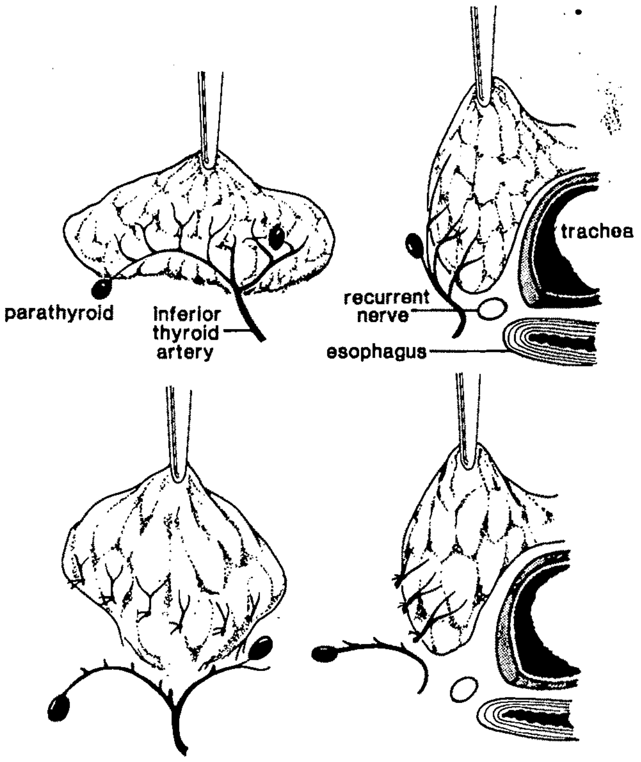

FIG. 1. Dissection used during the capsular technique for thyroidectomy, with ligation and division of the small tertiary vessels on the gland, preserving the blood supply to the parathyroid glands (adapted from Kurihara H, Takashi M. Safety of operation and indications for total thyroidectomy. Operation 1981; 35:1077–1086).

Results

Over the period from 1975 to 1985, 115 total thyroidectomies were performed for multinodular goiter. The progressive increase in the frequency with which total thyroidectomy has been performed for multinodular goiter is shown in Figure 2. It can be seen that, in 1975, there were 16 total thyroidectomies performed, and of these seven were for multinodular goiter. Over the subsequent 10 years, the number of total thyroidectomies for malignancy has remained virtually constant, whereas the overall number of thyroidectomies performed in our department has decreased.[9] On the other hand, there has been a progressive increase over the last 2 years in the number of total thyroidectomies (44 in 1985), and this has been entirely confined to operations for multinodular goiter.

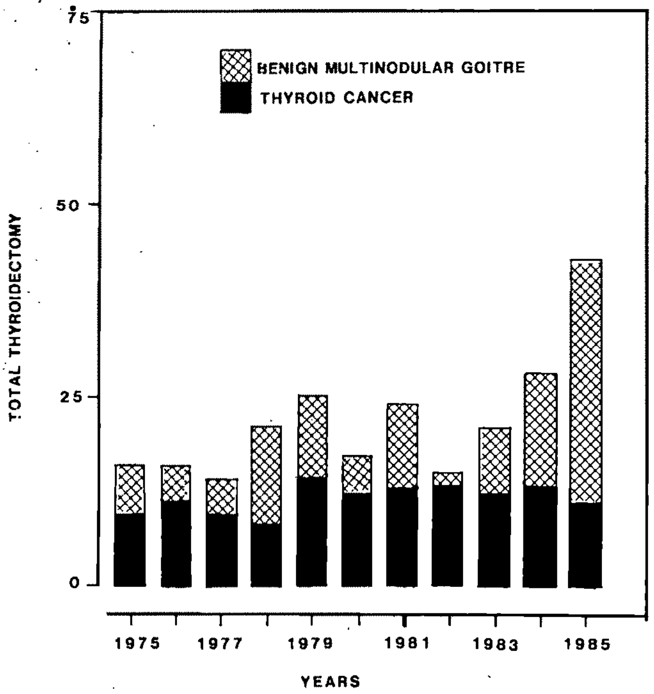

FIG. 2. Total thyroidectomies performed for both thyroid cancer and multinodular goiter during the period from 1975 to 1985.

Another way of looking at this changing practice is to examine operations performed specifically for multinodular goiter. These data are summarized in Figure 3, which shows the ratio of thyroidectomies (total *vs.* other procedures) performed for that condition over the last 10 years. Although the number of procedures overall for multinodular goiter has been relatively constant, the proportion of cases where a total thyroidectomy was performed has increased from 9% in 1975 to 50% in 1985.

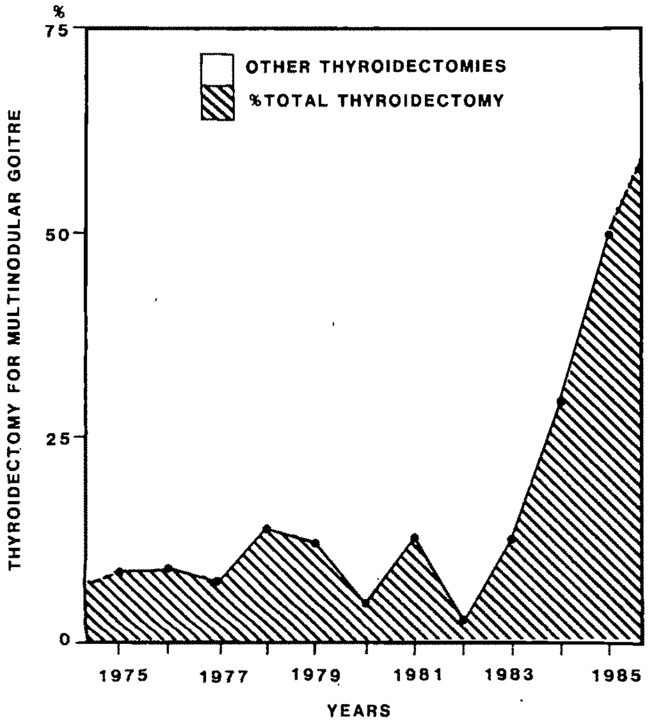

FIG. 3. Operations for multinodular goiter (1975–1985), showing the increasing percentage being performed as total thyroidectomies.

The complications of thyroidectomy for multinodular goiter are summarized in Table 1. These have been divided into two consecutive groups so that changing trends can be examined: 1975–1984 (789 thyroidectomies); and 1985 (64 thyroidectomies), by which time total thyroidectomy had become the established routine. There were two postoperative deaths overall, both resulting from cardiac causes. Before 1985, there were two cases of permanent hypoparathyroidism and one permanent recurrent laryngeal nerve palsy. All of these complications occurred in the group having a lesser procedure. There were no permanent complications when a total thyroidectomy was performed. There was no significant difference between the two groups with respect to temporary vocal cord dysfunction (normal cord function at extubation but subsequent impaired movement), temporary hypocalcemia, or postoperative hemorrhage/bruising. In 1985 there were no permanent complications in any group.

These figures compare more than favorably with the incidence of these complications in cases requiring reoperation for multinodular goiter. Within our own department (unpublished data) there has been a permanent recurrent laryngeal palsy rate of 3.1% and an incidence of permanent hypoparathyroidism of 3.7% after secondary thyroidectomy for multinodular goiter in 258 cases.

Discussion

Total thyroidectomy is an operation that continues to evoke considerable controversy, even in the management of conditions such as differentiated thyroid carcinoma,[1] in spite of the significant advantages in terms of this therapeutic option that can be demonstrated. When it comes to benign thyroid disease, total thyroidectomy has not been generally advocated, although some authors have recommended its use for Graves' disease (especially in patients with severe ophthalmopathy), thyroiditis, and nodular goiter. Indeed, in one review of 909 total thyroidectomies, less than one-quarter of the procedures were performed for thyroid cancer, the remainder being for benign thyroid disease.[3] The argument put forward by these authors was that, if total thyroidectomy can be performed as safely as lesser procedures for benign disease, then the indications for its use may be justifiably expanded to those situations where recurrent disease is a significant problem.

When dealing with multinodular goiter in particular, the surgeon commonly finds that there is no apparently normal thyroid tissue remaining. He or she must then choose between leaving abnormal thyroid tissue behind or performing a total thyroidectomy. The former approach carries with it the risk of recurrent disease, which may require subsequent re-operation, whereas the latter approach theoretically has the potential hazards of an increased risk of either permanent hypoparathyroidism or recurrent laryngeal nerve injury.

The incidence of permanent complications after thyroidectomy, total thyroidectomy in particular, varies considerably from center to center. In experienced hands, however, the incidence is acceptably low; for example, Clark[1] reports an incidence of 1% permanent hypoparathyroidism and no permanent recurrent laryngeal nerve damage in 82 consecutive total thyroidectomies. More than one-third of these were performed for benign thyroid disease. In 250 total thyroidectomies for nodular goiter, Perzik[3] reported an incidence of only 0.4% nerve injury and no hypoparathyroidism. This contrasted with 5% nerve injury and 3% hypoparathyroidism when the total thyroidectomy was performed for thyroid cancer. These latter complications were attributable to the more extensive surgery done because of the degree of spread of the malignancy rather than to operative technique. Other authors have reported that the incidence of complications increases as the complexity of the procedure increases; for example, Martensson and Terins[10] showed a progressive increase in the incidence of nerve injury from 5% for unilateral lobectomy up to 18% for total and subtotal lobectomy or 14% for total thyroidectomy.

In this study we have shown that total thyroidectomy for multinodular goiter can be performed with minimal complications. We believe that this results from the use of the technique of thyroidectomy as described, whereby dissection and ligation of the multiple vessels on the thyroid capsule preserve the blood supply of the parathyroids and minimize inadvertent injury to the recurrent laryngeal nerve.

On the other hand, the risks involved in re-operation for recurrent multinodular goiter are significantly greater than at the first operation. In our department this risk increases significantly, the rate of permanent nerve injury increasing to 3.1%, whereas that of permanent hypoparathyroidism is 3.7%. In other reports,[11] the risk of permanent nerve damage after secondary thyroidectomy for benign disease was 9.5%, whereas the risk of permanent hypoparathyroidism was 3.4%.

TABLE 1. *Complications of Thyroidectomy for Multinodal Goiter*

	1975–1984		1985	
	Total Thyroidectomy	Other	Total Thyroidectomy	Other
Deaths	0	2	0	0
Permanent complications				
Recurrent laryngeal nerve palsy	0	1	0	0
Hypoparathyroidism	0	2	0	0
Temporary complications				
Cord dysfunction	2	15	0	0
Hypocalcemia	10	11	0	1
Hemorrhage/bruise	4	16	0	1
Other	6	34	3	0
Total	83 (11%)	706	32 (50%)	32

When the entire gland is diseased in patients with multinodular goiter, a bilateral subtotal thyroidectomy, although reducing the bulk of the diseased tissue, is less than optimal treatment. Leaving a small portion of diseased gland is unlikely to prevent the need for long-term thyroxine replacement therapy, whereas attempts to suppress regrowth of that remaining gland by thyroxine do not guarantee success.[12] In performing a subtotal thyroidectomy it is also possible to leave behind the small posterior–lateral lobule of thyroid tissue that was first described by Zuckerkandl.[13] This tissue often extends into the retrotracheal retro-esophageal area, causing significant pressure symptoms. The presence of this lobule is frequently only recognized when the full mobilization necessary for a total thyroidectomy has been performed (Fig. 4).

We recommend, therefore, that total thyroidectomy is the procedure of choice for multinodular goiter where the entire gland is involved. It must be emphasized, however, that protection of the recurrent laryngeal nerve and parathyroid glands must still be paramount in

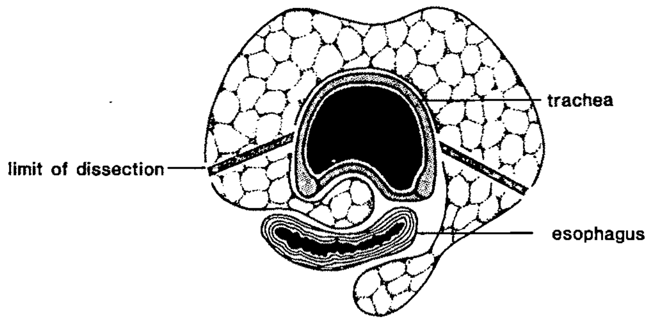

FIG. 4. Transverse section of the thyroid, showing the normal posterior limit of dissection during a bilateral subtotal thyroidectomy and its relationship to the posterior–lateral lobule.

dealing with benign thyroid disease. Ensuring such protection will, on occasion, require that minimal remnant thyroid tissue be left when anatomic vagaries render total excision of the gland less than totally safe. Of course, this policy requires that the operation be performed by an experienced surgeon who can guarantee that the procedure will be performed with minimal risk of complication.

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Motor Function in the Excluded Esophagus and Its Implications in the Management of Patients with Unresectable Carcinoma of the Esophagus

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Palliative exclusion of the esophagus by use of transposed stomach was performed in a 63-year-old woman with unresectable cervical esophageal cancer. Twelve weeks after this operation, motor function of the excluded esophagus was assessed. All voluntary swallows produced a motor response in the esophageal body. Eighty-five per cent of the contractions were peristaltic and generated mean pressures of 28 mmHg. Fiften per cent of the deglutitions were followed by nonpropulsive waves with mean pressures of 24 mmHg. Spontaneous tertiary activity occurred at a rate of 2.5 contractions per minute with an amplitude of 16 mmHg. Motor function in the excluded esophagus persists after bypass of the organ. This suggests that the excluded esophagus should be decompressed after surgery to prevent "blowout" of its closed ends.

WHEN THERE is a contraindication to esophageal resection for esophageal carcinoma, many patients are treated palliatively with a substernal or subcutaneous route to bring the stomach into the neck in order to totally exclude the esophagus.[1-5]

The fate of an excluded esophagus remains unclear. Both Johnson et al.[6] and Orringer[3] reported that the esophagus becomes an asymptomatic mucocele after exclusion. Similarly, Mannell reported on 51 patients who had total esophageal exclusion: in 20 of the 38 patients who had the esophagus closed at both ends, a mucocele was formed. Ninety-five per cent of the patients were asymptomatic, and the mucocele did not continue to increase in volume.[2] Experimentally, Deaton and Bradshaw[7] also described an isolated segment of the esophagus in which the cystic structure resulting from exclusion did not continue to increase in size.

Division of the esophageal musculature in the experimental animal does not interrupt peristalsis.[8,9] Similarly, transection of the esophagus with re-anastomosis or transection followed by a short jejunal or prosthesis interposition does not stop progression of a normal propulsive wave after voluntary swallowing.[5,8,10,11] Longhi and Jordan[12] and Janssens et al.[10,11,13] noted, however, that in dogs no primary peristalsis occurred in the excluded esophagus if the bolus was diverted away in the neck or even at the midesophageal level.

The purpose of this report is to document the motor function of an excluded esophagus that was bypassed for palliative reasons.

Case Report

History

A 63-year-old white woman with a significant history of alcohol consumption and tobacco smoking was investigated for cervical dysphagia, and she was found to have an esophageal epidermoid carcinoma. She was treated with curative radiotherapy (5500 rads in 22 sessions). However, her dysphagia did not improve, and she was referred when she had total esophageal obstruction. Endoscopic evaluation revealed neoplastic closure of the esophageal lumen 6 cm below the pharyngo-esophageal junction. Bronchoscopic examination showed posterior tracheal wall deformation without evidence of malignant cells from the tracheal mucosal brushings.

Surgical Procedure

Clinical staging suggested that the disease was confined locally. However, simultaneous exploratory laparotomy and neck exploration

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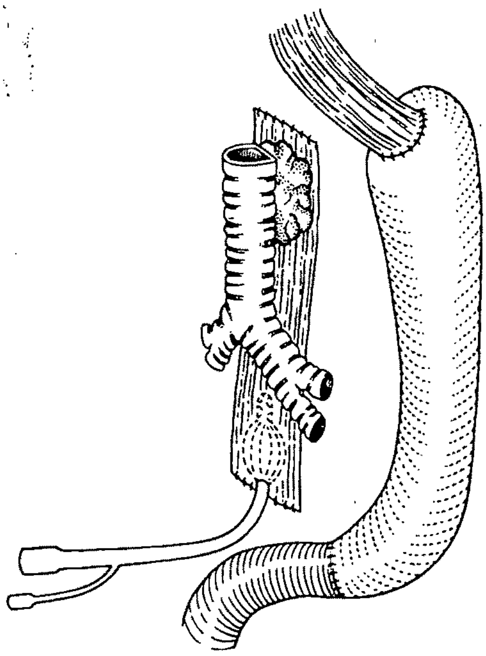

FIG. 1. Palliative esophageal bypass with esophageal exclusion. A fistula is created in the distal esophagus over a Foley catheter.

revealed a massive tumor obstructing the esophagus at the thoracic inlet. Posterior invasion of the trachea was present, with early left recurrent laryngeal nerve involvement, and resection was considered an inappropriate option. Esophageal exclusion was performed with the use of a substernal tunnel to bring the stomach up to the neck, and a cervical esophagogastrostomy was performed just below the proximal esophageal sphincter. A pyloroplasty was also performed. The excluded esophagus was decompressed by use of a #16 Foley catheter, which entered the esophageal lumen through the anterior wall of the esophagus immediately distal to the diaphragmatic hiatus. The catheter was brought out as a directed fistula under the right subcostal margin. The proximal esophagus was closed above the tumor (Fig. 1).

The patient was swallowing normally within a few days of operation, and there was minimal mucus drainage from the esophagus. Eight weeks after the operation, radiologic evaluation of the excluded esophagus was performed through the distal esophagostomy. The radioopaque material revealed multilevel simultaneous contractions in the esophageal body. Extravasation through the tumor and into the mediastinum was documented. After discharge the patient was comfortable for 9 months.

TABLE 1. *Motor Response of the Excluded Esophagus to Voluntary Swallowing*

Number of swallows	40
Resting intra-esophageal pressure	5
Percentage response	40/40
Primary waves	85
Tertiary waves in response to deglutition	15%
Spontaneous tertiary contractions	2.3/minute
Secondary waves	0%
Contraction pressures	
Primary waves	28 mmHg
Tertiary waves in response to deglutition	24 mmHg
Spontaneous tertiary contractions	16 mmHg

Manometric Evaluation

Twelve weeks after the bypass procedure, using the distal esophagostomy to introduce the motility catheter, motor function of the esophagus was evaluated with a standard manometric technique described previously.[14] Each one of the three lumina of the manometry catheter was perfused at a rate of 1.9 mL/min with a Harvard perfusion pump (Harvard Apparatus, Millis, MA). The perfused lumina were connected to three proximal transducers (H.P. Model 1280, Hewlett Packard, Corvallis, OR) and the recording made on a physiograph (H.P. 7754-A, Hewlett Packard). By instilling a 2-mL water bolus into the mouth, 40 voluntary swallows were induced in order to evaluate the function of the excluded esophagus.

Results

Motor function results in the excluded esophagus are shown in Table 1. The resting intra-esophageal pressure remained positive and ranged from 2 to 8 mmHg. All swallows were followed by a motor response in the esophageal body. Eighty-five per cent of the contractions were of the primary type, and 15% were nonpropulsive (Fig. 2). Between swallows, spontaneous tertiary contractions were observed at a rate of 2.5 contractions per minute. Contraction pressures were not high: the mean contraction value of the primary wave was 28 mmHg. Tertiary contractions in response to voluntary swallowing averaged 24 mmHg in amplitude. Mean contraction pressure for the spontaneous tertiary waves was 16 mmHg.

Discussion

If the esophagus is left in its normal position but is excluded from the alimentary tract, it can either be oversewn at both ends, with the reasoning that it will then become an asymptomatic "cyst," or it can be decompressed internally by a Roux-en-Y technique or externally by creation of a tube fistula. Such decompression allows continuous emptying of esophageal secretions and may prevent intraluminal pressure build-up if motor activity is present. There is no consensus on which of these approaches is best. At the beginning of the century, Kirschner advocated the use of a Roux-en-Y internal decompression.[5,14] More recently, Akiyama and Kiyama reported the cases of 11 such patients, and internal or external decompression was always added to the bypass procedure. No significant complications occurred.[15] Steiger et al.[16] presented 30 cases where the esophagus was excluded and decompressed by use of a Foley catheter. Mannell, in presenting her initial 10 cases, stated that five patients had total esophageal exclusion without decompression.[1] When compared with five other patients who had a Roux-en-Y internal drainage, no difference was observed between the two groups. More recently, Mannell and Epstein reported 51 patients with total esophageal exclusion without decompression.[2] Seventeen per cent of the patients had proximal esophageal disruption, and one patient had a distal esophageal leak. Twenty of 38 patients evaluated by computed tomography scanning had an esophageal mucocele develop. This was usually asymptomatic and not progressive. Orringer and Sloan reported their initial experience with 10 patients who had advanced carcinoma where the esophagus was excluded by simply closing it at both ends.[3] Their updated experience with this approach reveals 17% of distal esophageal disruption.[4]

Experimentally, after removing the esophageal muscularis externa, Meltzer showed that primary peristalsis was not interrupted.[9] Surgical transection and re-anastomosis was studied by Carveth et al., who similarly showed that this operation did not stop the progression of the primary esophageal waves.[8] Greenwood performed short intestinal interpositions and short prosthetic interposition at midesophageal level and showed that primary peristalsis "jumped" these interposed segments to continue into the distal portion of the esophagus.[17]

In a different set of experiments in animals, Longhi and Jordan[12] diverted the esophagus at the cervical level and reported that no deglutitive contractions occurred below the level of bolus deviation. Janssens et al.[10,11,13] created a cervical esophageal diversion and a midthoracic esophageal diversion and took electromyographic recordings of both the proximal and distal segments. They reported that when the esophagus was diverted in the neck, deglutition with a bolus elicited a normal response in the esophageal segment above the transection, but there was no peristaltic sequence seen in the thoracic esophagus below the transection. When the diversion was at the midesophageal level, electromyographic activity was recorded in both the proximal and distal half of the esophagus. These investigators suggested that when there were no afferent impulses from the bolus, the central regulating mechanism was not sufficiently coordinated to guarantee peristaltic contractions. Their main conclusion was that primary peristalsis is entirely bolus dependent in its course through the cervical esophagus.

However, despite diversion of the esophagus at the cervical level immediately distal to the upper esophageal sphincter in our patient, the 40 swallows invariably produced a motor responses in the totally excluded esophageal body. Eighty-five per cent of these responses were peristaltic. Local factors such as the presence of carcinoma in the cervical esophagus, the irradiation to the tumor area, and operation followed by proximal mediastinal infection may have accounted for the 15% tertiary contractions that were observed after voluntary swallows. Similarly, the high incidence of spontaneous tertiary activity between deglutitions may have resulted from similar local factors. The small perfusion volume (1.9 mL/min/lumen) used for the manometric recording may have been an additional factor. The implication of these observations is that when the esophagus is totally excluded and left in place, intact organized motor function persists in the esophageal body. It is highly likely that this activity was coordinated *via* the vagi,[18] which were left intact in our patient.

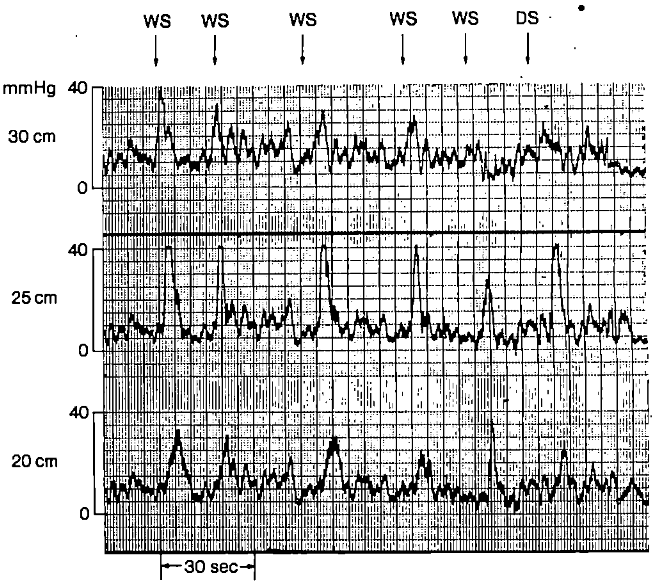

FIG. 2. Primary and tertiary contractions in the excluded esophagus in response to voluntary swallowing (WS = wet swallow). The distances are measured from the skin orifice of the fistula.

Complications do not result in all patients when the esophagus is closed at both ends. This may relate to the strength of esophageal contractions that occur, because it has been reported that an obstructed esophagus can lose its peristaltic activity.[19,20] However, the fact that peristaltic activity may be retained suggests that it is probably safer to use esophageal decompression to prevent disruption of a proximal or distal esophageal closure line.

In conclusion, it appears that when total esophageal diversion is performed in the neck, the excluded esophagus may retain its motor activity. Decompression of the excluded esophagus should be performed in order to prevent complications resulting from this retained activity.

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Efficacy of Cefazolin, Cefamandole, and Gentamicin as Prophylactic Agents in Cardiac Surgery

Results of a Prospective, Randomized, Double-blind Trial in 1030 Patients

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In an effort to develop an improved regimen of antibiotic prophylaxis in cardiac surgery, 1030 patients who were to have elective cardiothoracic surgery involving a median sternotomy were selected at random to receive cefamandole or cefazolin, with or without gentamicin, in a prospective double-blind study. Cefazolin was significantly less effective than cefamandole at both the sternal (1.8% *vs.* 0.4%, respectively, $p < 0.05$) and donor sites (1.3% *vs.* 0%, respectively, $p < 0.02$). Seven *Staphylococcus aureus* infections occurred among cefazolin recipients as compared with no such infections among the patients receiving cefamandole ($p < 0.01$). All five wound infections yielding fungi or gentamicin-resistant gram-negative rods occurred in patients who had received gentamicin as a second prophylactic agent. These data suggest that gentamicin has no role as a prophylactic antibiotic in cardiac surgery and that, compared with cefamandole, cefazolin offers unreliable prophylaxis against deep infection at both the sternal and donor sites.

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PROPHYLACTIC ANTIBIOTICS have proven effective in lowering wound infection rates after cardiac surgery,[1,2] and most cardiovascular surgeons routinely use one or more antibiotics during the perioperative period. However, despite administration of prophylactic antibiotics, infections in both the sternal and donor sites continue to occur in 1–5% of patients, and controversy exists regarding the optimal prophylactic regimen.[3–6]

Since 1978, more than 1000 median sternotomies have been performed each year at Saint Thomas Hospital. Perioperative cefazolin has been the mainstay of prophylaxis. The deep sternal wound and donor site infection rates have each averaged approximately 2% for the last 5 years. The pathogen spectrum has remained relatively constant over this period of time. *Staphylococcus aureus* has accounted for approximately 40% of pathogens in sternal wounds and coagulase-negative staphylococcus, 25%. Enteric gram-negative rods, fungi, and mixed pathogens have accounted for the remainder of the identifiable pathogens.

Since the early 1980s, several studies had indicated that cefamandole was the most active cephalosporin against coagulase-negative staphylococci *in vitro.*[7–9] The clinical relevance of this finding remains unknown. Because coagulase-negative staphylococci were known to be a common pathogen in sternal wound sites in our hospital, a prospective, randomized, blinded study comparing cefamandole with the most commonly used prophylactic antibiotic, cefazolin, was instituted in November 1984. Because cephalosporin-resistant pathogens accounted for approximately one-fifth of such infections, gentamicin was also included in this trial.

Materials and Methods

Antibiotic Regimens

Using block randomization, patients were assigned to one of four prophylactic regimens. Regimen A consisted of cefazolin, 2 g intravenously (I.V.) at induction of anesthesia, 1 g every 4 hours during operation, and 1 g every 6 hours after operation for 72 hours. Regimen B included cefazolin as outlined above, plus gentamicin

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1.5 mg/kg given I.V. at the induction of anesthesia. Regimen C was cefamandole, 2 g I.V. at induction of anesthesia, 1 g every 2 hours during operation, and 1 g every 4 hours after operation for 72 hours. Regimen D included cefamandole as above, except that gentamicin 1.5 mg/kg was given I.V. at the induction of anesthesia. No dose adjustments were made for renal failure. Placebo doses were not included. All randomization was performed by one investigator (A.C.R.). Drugs were dispensed in minibags labeled "Mancef" and marked with time for infusion.

Definition of Infection

Wounds were considered infected if (1) purulence was present; and (2) deep subcutaneous tissue (Class II infection), sternum (Class III infection), or posterior mediastinum (Class IV infection) was involved. Class I or superficial infections of the subcutaneous tissue of the sternum or donor site were not included. By definition, such infections appeared trivial upon inspection, and neither prolonged hospitalization nor altered outpatient management was required. Class I sternal infections were tabulated prospectively, however. When the code was broken at the close of the study, the Class I infections were noted to be evenly distributed among the four prophylactic regimens. One Class I infection occurred among regimen A recipients, three among regimen B recipients, two among regimen C recipients, and three among regimen D recipients.

At 3-month intervals, the attending surgeon, at least one other cardiac surgeon investigator, and one nonsurgeon member of the investigative team (A.B.K.) reviewed the clinical course of all patients with wounds exhibiting inflammation and/or drainage. An agreement was reached as to the presence or absence of infection and the depth of infection. Care was also taken at this time to exclude patients with secondary infections in the sternal area that may have developed as a complication of ischemic necrosis of the underlying tissue. One such patient, who was eventually identified as a regimen B recipient, met this criterion and was excluded. She was a 63-year-old patient with long-standing Raynaud's disease and was receiving steroid therapy; she experienced necrosis of the entire hemisternum associated with the use of the ipsilateral internal mammary artery for implantation. According to protocol design, after approximately 1000 patients had been studied, antibiotic regimens associated with infections were identified with a letter code by the pharmacist. At that time, in January 1986, a significant difference in treatment categories was noted. The code was subsequently broken, and the study ended.

Patient Selection

The study design was approved by the Saint Thomas Hospital Institutional Review Board. Written informed consent was obtained from all participants. All adult patients scheduled for elective median sternotomy incision who were free of infection and not receiving any therapeutic antibiotics were considered eligible for inclusion in the study. To remain in the study, patients had to adhere to the antibiotic protocol for at least 24 hours.

All patients showered or bathed with an antiseptic-containing soap the evening before operation. Shaving of the operative site(s) was performed in the holding area immediately before operation. The mediastinum was routinely irrigated with a kanamycin solution (1 g/L of saline) before closure.

Drug Levels

Early in the course of this study, an average of seven plasma specimens per patient were obtained from 25 patients during the operative period. Specimens were frozen at −20 C and shipped to Eli Lilly Laboratories for analysis. Gentamicin levels were analyzed by radioimmunoassay techniques. Cefamandole and cefazolin plasma levels were measured by bioassay. Antibiotic levels were plotted against time on semilog paper and the best straight line determined. The lowest intraoperative serum concentration of antibiotic (usually occurring immediately before antibiotic redosing) was estimated from this plot.

Cost Analysis

Seven of 11 patients with sternal wound infection and five of the six patients with donor site infection had evidence of infection develop after discharge and were re-admitted to Saint Thomas Hospital specifically for management of the infections. All re-admission hospital charges for these 12 patients were considered to be direct costs of infection. For the patients whose wound infections developed before discharge, the charges were considered to be secondary to infection only during the portion of the hospital stay that was clearly prolonged as a result of infection.

Risk Analysis

Demographic data on patients who had cardiac surgery at Saint Thomas Hospital are maintained by an in-office minicomputer. Host risk factors and intra-operative and postoperative complications are identified on work sheets by physician assistants. All such infor-

TABLE 1. *Sternal and Donor Site Infection Rates in Cardiothoracic Surgery: A Comparison of the Efficacy of Prophylactic Antibiotics*

Prophylactic Antibiotics	Patients Who Had Median Sternotomy	Sternal Wound Infections (%)	Patients Requiring Donor Site Incision*	Donor Site Infections (%)
Cefazolin	255	3 (1.2)	239	4 (1.7)
Cefazolin–gentamicin	253	6 (2.4)†	236	2 (0.8)
Cefamandole	259	2 (0.8)	246	0 (0)
Cefamandole–gentamicin	263	0 (0)†	242	0 (0)
Total	1030	11 (1.1)	963	6 (0.6)
All cefazolin	508	9 (1.8)‡	475	6 (1.3)†
All cefamandole	522	2 (0.4)‡	488	0 (0)†
Total	1030	11 (1.1)	963	6 (0.6)
With gentamicin	516	6 (1.2)	478	2 (0.4)
Without gentamicin	514	5 (1.0)	485	4 (0.8)
Total	1030	11 (1.1)	963	6 (0.6)

* Includes those patients who had coronary artery bypass and required a leg incision for the harvesting of saphenous vein.

† Difference in infection rates is significant at $p < 0.02$, Fisher's exact test.

‡ Difference in infection rates is significant at $p < 0.05$, Fisher's exact test.

mation is obtained at the time of hospitalization and entered prospectively into the computer program. These data were available for analysis for patients entered into the study. Age and the presence of diabetes mellitus, obesity, hypertension, use of internal mammary arteries in coronary artery bypass, perfusion time, and cross-clamp time were tabulated. All statistical tests for association of frequencies (contingency table analysis) were performed by chi square analysis or by Fisher's exact test when expected frequencies were less than five.

Results

Patient Demographics and Risk Factors

Of 1446 patients who had median sternotomy at Saint Thomas Hospital from November 1984 through January 1986, 1057 (73%) were entered into the study. Operations were subsequently canceled for 11 patients, and nine patients were removed from the study for failure to adhere to the antibiotic regimen for the first 24 hours. Seven patients scheduled for thoracic surgery not involving a median sternotomy were inadvertently entered into the study and were later removed. The 27 patients excluded from the study after entry were evenly distributed among the four prophylactic regimen groups.

A total of 1030 patients were therefore available for evaluation. Of these patients, 57 had median sternotomy for valve replacement only, 44 for valve replacement and coronary artery bypass, 919 for coronary artery bypass alone, and 10 for other cardiac surgical procedures. During this period of time, 389 patients had median sternotomy but were not considered for the study. Nine sternal wound infections determined retrospectively by routine nosocomial surveillance occurred among the patients who were not from the study, for an infection rate of 2.2%. Cefazolin was usually given as a prophylactic agent in these patients who were not from the study, although cefamandole and vancomycin, with or without gentamicin, were also used occasionally.

An analysis of infections by the seven participating surgeons demonstrated no significant difference in surgeon-specific infection rates. All risk factors were homogeneously distributed among the four treatment regimens, between patients receiving cefazolin *versus* cefamandole, and between patients receiving gentamicin *versus* no gentamicin. There were no cases of prosthetic valve endocarditis among the 101 patients who had valve replacement.

Efficacy of Prophylaxis

Sternal wound infections developed in 11 of the 1030 patients who had elective median sternotomy (Table 1). Donor site infections developed in six of 963 patients requiring a donor site incision. Patients receiving cefamandole–gentamicin had a significantly lower sternal wound infection rate than those receiving cefazolin–gentamicin (0% and 2.4%, respectively; $p < 0.02$). When infection rates for the regimens that included gentamicin are compared with rates for those that did not, the results are virtually identical (1.2% *vs.* 1.0%). When the results were analyzed by individual cephalosporins, patients receiving cefamandole with or without gentamicin had a significantly lower infection rate than patients receiving cefazolin with or without gentamicin at both the sternal (0.4% *vs.* 1.8%, $p < 0.05$) and donor sites (0% *vs.* 1.3%, $p < 0.02$).

TABLE 2. *Pathogens, Class of Infection, and Prophylaxis Regimen*

	Sternal Infections		Donor Site Infections	
Antibiotic Regimen	Patient No.*/ Class of Infection	Pathogen(s)†	Patient No./Class of Infection	Pathogen(s)
Cefazolin	1/III	*Staphylococcus aureus* (M, K)	12/II	*S. aureus;* CNS; enterococci
	2/III	*S. aureus*	13/II	*Escherichia coli;* enterococci
	3/II	CNS (M, K, G)	14/II	*S. aureus*
			15/II	*S. aureus; Proteus mirabilis*
Cefazolin/gentamicin	4/II	*S. aureus*	16/II	Pseudomonas (K, G); Proteus
	5/III	*S. aureus* Citrobacter (K, G)		Klebsiella
	6/II	CNS (M, K, G) Pseudomonas (K)	17/II	Pseudomonas (K, G)
	7/III	Pseudallesheria		
	8/IV	*Candida tropicalis*		
	9/II	*E. coli*		
Cefamandole	10/II	CNS (M, K, G)		
	11/II	(No growth)		

* All patients had coronary artery bypass surgery (CAB) except patients 5 (ventricular aneurysmectomy) and 7 (CAB plus aortic valve replacement).

† Resistance (if present) to cefazolin/cefamandole (K) is noted within parentheses. Coagulase-negative staphylococci (CNS) and *S. aureus* were also tested for resistance to methicillin (M); and gram-negative rods were tested to resistance to gentamicin (G). All *S. aureus* infections were resistant to penicillin. Susceptibility testing was performed by standard Kirby-Bauer sensitivity testing.

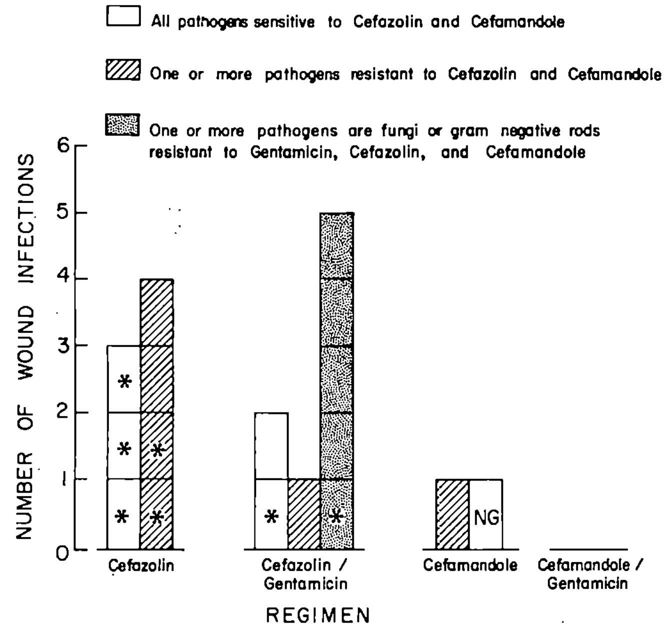

FIG. 1. Correlation of prophylactic antibiotics and antimicrobial resistance of pathogens. One infection in a cefamandole recipient yielded no growth (NG) on culture. All infections yielding *S. aureus* (denoted by an asterisk) occurred among cefazolin or cefazolin–gentamicin recipients. Resistance of fungi and gram-negative rods to cefazolin–cefamandole and gentamicin occurred only in cefazolin–gentamicin recipients. No infections occurred among cefamandole–gentamicin recipients.

Infecting Organism

All seven wound infections yielding *S. aureus* (four sternal and three donor sites) occurred in patients receiving cefazolin as a prophylactic agent (seven of 508 cefazolin recipients *vs.* none of 522 cefamandole recipients, $p < 0.01$). Coagulase-negative staphylococci as a single or co-infecting pathogen were identified in three sternal wound sites and one donor site. Three of these infections occurred in patients receiving cefazolin (Table 2). In five wound infections, all pathogens isolated were susceptible to both cefazolin and cefamandole (Fig. 1). All of these infections occurred in recipients of cefazolin or cefazolin–gentamicin (five of 508 cefazolin recipients *vs.* none of 522 cefamandole recipients, $p < 0.05$). Of five wound infections yielding gram-negative bacilli resistant to gentamicin (3) or fungi (2), all occurred in patients who had received gentamicin in addition to cefazolin as a prophylactic agent.

Pharmacokinetics

Intra-operative antibiotic levels were measured in 12 patients receiving cefazolin, 13 receiving cefamandole, and 14 receiving gentamicin. The mean trough levels of antibiotics during the bypass procedure averaged 39 μg/mL for cefazolin, 21 μg/mL for cefamandole, and 1.5 μg/mL for gentamicin. However, the trough levels ranged widely among patients. For cefazolin recipients, the lowest trough plasma concentration was 22 μg/mL. For the cefamandole recipients, the lowest trough concentration was 11 μg/mL, and for the gentamicin recipients, 0.7 μg/mL. By the close of the surgical procedure, gentamicin levels in gentamicin recipients were negligible.

Infection Complications and Costs

The excess costs of hospitalization attributable to infection are outlined in Table 3. Among the six patients with Class II infections of the sternal wound, two infections resulted in prolongation of hospitalization and three in re-admission to Saint Thomas Hospital. One patient was managed by repeated incision and drainage of the infection in the physician's office. All Class III and Class IV infections at the sternal site occurred among cefazolin or cefazolin–gentamicin recipients. Three patients with Class III infections of the sternum required re-admission to the hospital; the fourth patient's primary hospitalization was prolonged extensively. A Class IV infection developed in one patient during the initial hospitalization. This patient eventually died of multiple complications. Five of the six deep (Class II) infections occurring at the donor sites resulted in rehospitalization. The average cost of donor site infections was $8500, an amount similar to the $9000 cost of Class II infection at the sternal incision site. Physician fees and office charges related to both sternal and donor site infections were not determined.

TABLE 3. *Excess Cost of Hospitalization Attributable to Infection*

Depth of Infection (No. Patients)	Total Excess Costs ($)	Mean Excess Cost ($)
Sternal site		
Class II (6)*	53,500	8,900
Class III (4)	160,200	40,000
Class IV (1)	73,300	73,300
All sternal sites (11)	287,000	26,000
Donor site		
Class II (6)	51,000	8,500
All sites (17)	338,000	19,882

* Both infections associated with cefamandole prophylaxis were Class II infections.

Discussion

A primary goal of the design of this study was to evaluate the relative efficacy of cefamandole *versus* cefazolin in preventing infection resulting from coagulase-negative staphylococci. Although three of the four infections yielding coagulase-negative staphylococci occurred in cefazolin recipients, infections resulting from coagulase-negative staphylococci were too infrequent to allow conclusions to be drawn regarding the relative efficacy of these two cephalosporins. One can only speculate as to whether a significant advantage of cefamandole *versus* cefazolin could be demonstrated in a setting where coagulase-negative staphylococci were a more frequent cause of postsurgical wound infection.

Of great interest, however, was the finding that infections resulting from *S. aureus* were significantly less likely to occur among the cefamandole recipients. Even if the one infection resulting from a methicillin-resistant *S. aureus* in a cefazolin recipient is not included in the analysis, significantly more *S. aureus* infections occurred among cefazolin recipients than among cefamandole recipients ($p < 0.02$). Slama et al. also recently noted that cefazolin tended to be less effective in preventing *S. aureus* infection after cardiac surgery than either cefamandole or cefuroxime.[6] *In vitro* studies are not currently available that directly explain why cefamandole should prevent *S. aureus* infection more effectively than cefazolin. As early as 1973, however, failures of cefazolin in treating infection resulting from *S. aureus* have been reported.[10,11] Although the precise cause of this phenomenon remains unexplained, a number of investigators have noted that cefazolin appeared to be more vulnerable to hydrolysis by the beta-lactamase of certain *S. aureus* strains than either cefamandole or cephalothin.[12–16] Cefamandole has also been shown experimentally to produce higher concentrations than either cefazolin or cephalothin in fibrin clots.[17,18] Clinically, prophylactic use of cefamandole has been shown to result in high concentrations of antibiotic in atrial muscle and cardiac valve tissues.[19] Whether the inferior performance of cefazolin is related to its vulnerability to *S. aureus* beta-lactamase, to inferior tissue levels, or to other factors is unknown. Whatever the reason(s), data are accumulating to suggest that cefazolin may not be as reliable as other cephalosporins in prophylaxis of wound infection in cardiac surgery.

One conclusion of our study was that gentamicin, when given as a single preoperative dose, offered no protection from infection resulting from cephalosporin–resistant pathogens. Although gentamicin combined with cefamandole was the most effective of the four prophylactic regimens, an analysis of infection rates of the various antibiotic combinations (Table 2) suggests that it was the use of cefamandole *per se*, not cefamandole plus gentamicin, that best explained the observed differences in infection rates. Another interpretation of the apparent lack of gentamicin effectiveness may be related to the use of kanamycin irrigation in all patients. Although there are inadequate data to settle the issue, topical kanamycin may, in fact, be as efficacious as systemically administered gentamicin, thereby blunting any possible demonstration of the latter's efficacy.

However, it was of considerable interest to note that all infections resulting from cephalosporin-resistant (Patient 6) or cephalosporin and gentamicin-resistant (Patients 5, 16, and 17) gram-negative enteric pathogens occurred in patients receiving gentamicin as a second prophylactic agent. Moreover, both fungal infections occurred in gentamicin recipients (Patients 7 and 8). This failure/adverse effect of gentamicin was disappointing but not completely unexpected. Gentamicin has yet to be proven effective as a prophylactic agent in prospective clinical trials in clean surgery.[20] Furthermore, a previous study in cardiac surgery suggested that the routine use of gentamicin prophylaxis can be associated with a marked increase in gentamicin resistance within the hospital environment.[21] Given the fact that plasma levels were uniformly low in all patients at the close of operation, an observation noted previously,[22] it may be that prophylactic efficacy cannot be realized unless frequent doses of this agent are given. The threat of ototoxicity or nephrotoxicity associated with repeated doses must, however, serve as a caution, if not a deterrent, in designing prospective clinical trials involving frequent doses of gentamicin.

Because failure of prophylaxis in cardiothoracic surgery has been related to inadequate serum levels at the close of prolonged procedures,[4,23] we administered intraoperative doses of cefamandole and cefazolin so that adequate levels of these cephalosporins would be maintained throughout the surgical procedure. The results of our cephalosporin serum assays obtained during cardiopulmonary bypass were consistent with the findings of others.[24–27] Based upon these data, cefazolin dosing intervals might safely be lengthened to 6 or 8 hours. However, pending collection of additional data, frequent doses of cefamandole (every 2 hours) should be used during bypass if predictably high levels are to be achieved throughout the surgical procedure.

In May 1986, cardiac surgeons at Saint Thomas Hospital changed from the predominant use of cefazolin to cefamandole. Subsequent to this change, only eight deep sternal wound infections have developed among 1131 patients (infection rate, 0.7%). Five deep donor site infections have also occurred during this time. *S. aureus* has been isolated from four of these 13 infections. These follow-up data suggest that cefamandole continues to be preferred to cefazolin for prophylaxis of cardiac surgery in our hospital.

In view of these results, single-dose gentamicin, as an adjunct to cephalosporin prophylaxis, probably has no place in routine prophylaxis in cardiac surgery. Efficacy has not been demonstrated, and there is a suggestion that the use of gentamicin prophylactically may encourage the emergence of resistant organisms. Whether multiple dosing of gentamicin or the use of other broad-spectrum antibiotics would be effective in preventing gram-negative rod infection is unknown. The apparent failure of cefazolin in preventing wound infection, especially infection resulting from *S. aureus,* has important implications in view of the widespread current use of this antibiotic. Cefazolin has clearly demonstrated its effectiveness as a prophylactic agent in a wide variety of clean and clean-contaminated surgical procedures.[20] Nevertheless, this study and the recent study by Slama et al.[6] have now demonstrated its inferiority to other cephalosporins in prophylaxis of wound infections in cardiac surgery.

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Cardiac Cryolesions as an Experimental Model of Myocardial Wound Healing

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The standard coronary ligation model for experimental myocardial infarction results in variable areas and patterns of necrosis; therefore, the healing of such infarctions is also variable. The authors developed an experimental myocardial injury model using simple cryoinjury, which allows standardization of the size, depth, and location of the wound. Thirty-eight left ventricular cryolesions were created in 19 dogs, which were then killed from 3 to 35 days after injury. A consistent decrease in the depth of scar ($p < 0.005$) and accumulation of collagen ($p < 0.0001$) over time characterized this healing myocardial wound. Histologic examination revealed that the cellular pattern of healing myocardial cryolesions is similar to that of a healing myocardial infarction but with less variability. The authors advocate the use of cardiac cryolesions as a model of experimental myocardial wound healing.

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DESCRIPTIONS of the histopathologic evolution of myocardial infarction attribute little active role to the pericardium. In a study of 192 autopsies, Fishbein et al.[1] mentioned some endocardial and pericardial fibrosis adjacent to the infarcted myocardium. Cardiac surgeons frequently encounter pericardial adhesions in patients with healed myocardial infarctions and those who have had previous cardiac surgical procedures. In fact, recent enthusiasm has arisen for using artificial pericardial substitutes to minimize adhesion formation in an attempt to facilitate reoperation.[2] The role of the pericardium in myocardial wound healing, however, remains incompletely characterized.

One of the difficulties in studying myocardial wound healing is the variability induced in creation of the wound. Experimental myocardial infarction is usually produced by ligation of coronary arteries, with or without injecting the vessel with foreign substances.[3] Unfortunately, the extent of infarction produced depends on the coronary arterial anatomy supplying this region of the ventricle (which is variable) and the (equally variable) collateral arterial supply. Another limitation of this technique is the 20–40% early attrition associated with creation of the infarct,[4] usually resulting from ventricular tachyarrhythmias.

Cardiac cryolesions were first described by Hass in 1948[5] and have recently been used as an ablative technique in the surgical treatment of arrhythmias.[6] Cryolesions reportedly heal into a firm scar with little disruption of surrounding myocardial anatomy; furthermore, arrhythmias are rare after creation of cryolesions, and abnormal degrees of ventricular ectopy are not present a week after freezing.[7] Because cryolesions should represent reproducible, nonarrhythmogenic areas of myocardial necrosis, we studied such cryolesions as an experimental model of myocardial wound healing.

Methods

Nineteen adult mongrel dogs of both sexes (14–31 kg) were anesthetized with intravenous pentobarbital (30 mg/kg), intubated, and placed on a Harvard ventilator. Electrocardiograms were continuously monitored. The heart was exposed through a right thoracotomy performed through the fifth intercostal space. The pericardium was opened longitudinally, and the heart was de-

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livered from the pericardial sac. All animals received humane care in compliance with "Principles of Laboratory Animal Care," formulated by the National Society for Medical Research, and the "Guide for the Care and Use of Laboratory Animals," prepared by the National Academy of Science and published by the National Institutes of Health (NIH Publication 80-23, revised 1978); this protocol was approved by the Palo Alto Veterans Administration Medical Center Animal Research Committee.

Cryolesions were produced by cooling a pure copper rod (15 mm in diameter and 175 mm in length) in a bath of dry ice and acetone. When the rod ceased to produce bubbles in the dry ice/acetone bath, it was manually held on the surface of the left ventricular myocardium for 2 minutes. The area of frozen myocardium thawed over a period of 5 minutes, assuming a cyanotic color and contracting less vigorously. When the cryolesion had thawed, the copper rod was again used to freeze the same area of myocardium for an additional 2 minutes. A second area of myocardium, at least 2 cm from the first, was then injured with the same "double-freeze" technique. Two lesions were made on each left ventricle. During the period of thawing, arterial bleeding was occasionally observed, but it spontaneously ceased after several minutes.

A sterile surgical glove (latex rubber) was rinsed in normal saline and then cut into circular pieces (3 cm diameter). A piece of latex was then sutured around one of the cryolesions (chosen at random) with the use of a continuous 4–0 polypropylene suture, and the heart was replaced in the pericardial sac. The pericardium was closed with the use of continuous 3–0 chromic suture. Chest tubes were placed and the incision closed in standard fashion.

Animals were killed at 3 days and 1, 2, 3, and 5 weeks. Hearts were removed *en bloc* with the surrounding pericardium. The degree and extent of attachment of the pericardium to the exposed (bare) cryolesions and those covered by the latex rubber patches were recorded as the pericardium was dissected free from the myocardium. The physical dimensions of the healing lesions were recorded. A full-thickness sample of myocardium containing the cryolesions was removed with a cuff of normal myocardium and placed in 10% formalin. After fixation, a 1-mm (True-Cut) needle biopsy was performed through the center of each cryolesion for hydroxyproline analysis, and a transverse, transmural section of the cryolesion was processed, embedded in paraffin, and stained with hematoxylin and eosin or Masson's trichrome.

The transmural biopsy specimens were heated at 60 C for 48 hours, weighed, and then hydrolyzed for 18 hours in 6 N HCl at 110 C. The specimens were then dried and resuspended in a known volume of water. Total hydroxyproline was measured with the Technicon Auto Analyzer.[11] Standards of known collagen content were routinely run with this assay. Statistical analysis was performed by use of the two-way analysis of variance (ANOVA), followed by appropriate paired and unpaired t-tests.

Results

Creation of cryolesions did not result in prolonged arrhythmias, but touching the ventricle with the cold copper rod precipitated transient sinus tachycardia (which resolved after rod removal) in several dogs. The dogs were continuously monitored for 2 hours after creation of the lesions; only occasional premature ventricular beats were noted. All animals survived creation of the myocardial cryolesion and the intended postoperative follow-up interval. Ventricular fibrillation developed in one additional animal before myocardial freezing, and the dog was excluded from the study.

The pericardium was not attached to the exposed cryolesion or to the latex patch in any of the dogs killed at 3 days. By 7 days, the pericardium had become attached to most of the exposed cryolesions and to the myocardium surrounding the latex patch in two of the four dogs in this group. Interestingly, in these two dogs without adherence to the area surrounding the latex rubber patches, the pericardium was also not adherent to the exposed cryolesions. In dogs killed after 14 days, the pericardium was adherent to both the exposed cryolesions and the myocardium surrounding the latex patches in all dogs. In one of the four dogs killed at 21 days, the pericardium was not adherent to either lesion. The pericardium in both dogs killed at 5 weeks was adherent to the surgically created wounds.

The dimensions of the cryolesions were analyzed according to treatment group (latex rubber patch *vs.* no patch), but no significant differences were found between groups. The depth of the exposed cryolesions decreased from 5.5 ± 0.4 mm (mean ± standard error of the mean [SEM]) on day 3 to 0.9 ± 0.1 mm on day 35, whereas the depth of the patched cryolesions decreased from 6.2 ± 0.3 to 0.9 ± 0.1 during the same period. Because the depth of lesion was not dependent on the presence or absence of the pericardium, the data from both groups were combined. Analyzed together, the depth of the cryolesions was inversely related to postoperative time ($r = -0.91$, $p < 0.0001$, SEE = 0.746 [Fig. 1]).

The collagen content (as assessed by transmural biopsy hydroxyproline levels) of the cryolesions exposed to the pericardium increased from 35.5 ± 8.0 μg/mg dry weight at 3 days to 212 ± 20 μg/mg at 35 days. The

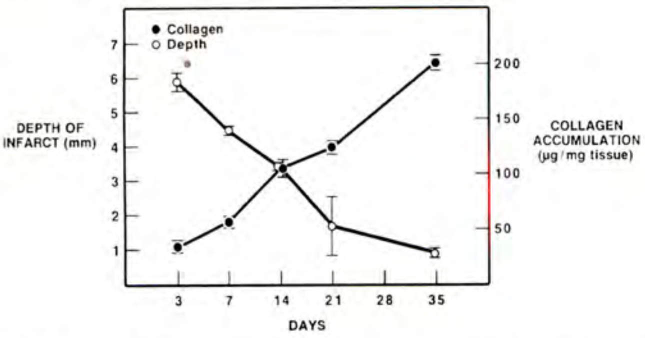

FIG. 1. Depth of cryoinjury "scar" decreased while collagen accumulation increased during 5 weeks of observation. Variability expressed as plus or minus 1 standard error of the mean.

collagen content of the cryolesions that were patched with latex ranged from 32 ± 8 to 190 ± 7 during the same period. Because collagen accumulation in the cryolesions did not differ significantly between the two groups, these data were also combined. When all cryolesions were analyzed, collagen accumulation in healing cryolesions correlated strongly with time ($r = 0.89$, $p < 0.0001$, SEE = 19.22 [Fig. 1]).

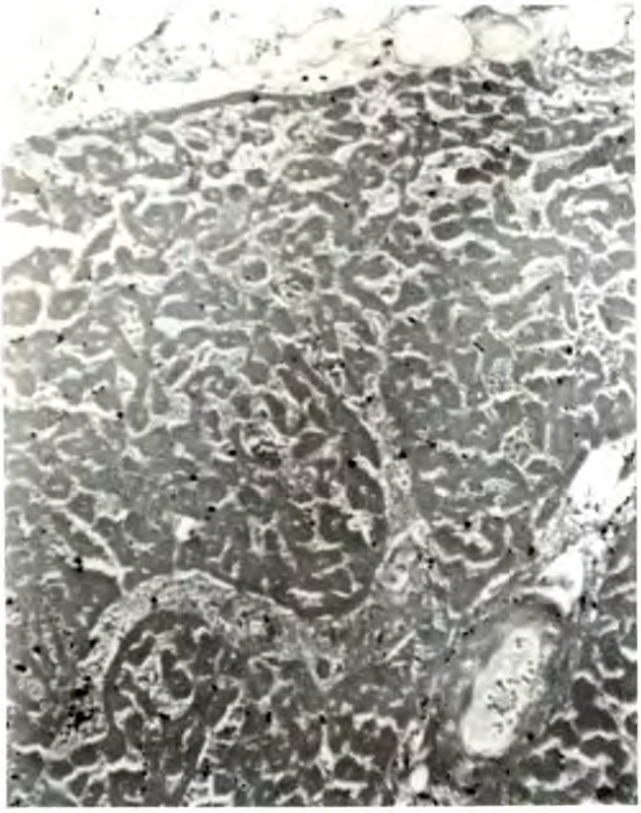

FIG. 2. Canine left ventricle 3 days after cryoinjury. Note epicardium above and coagulative necrosis of underlying myocardium (hematoxylin and eosin, original magnification ×200).

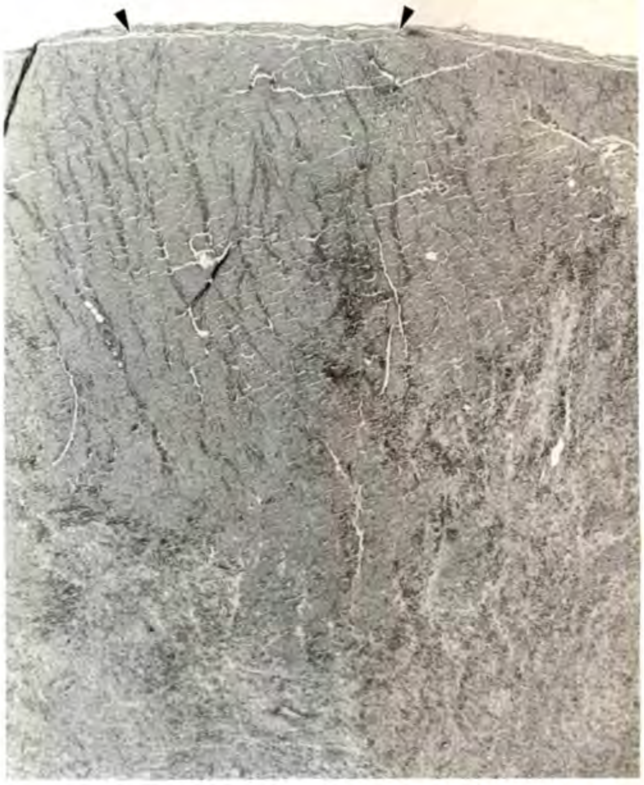

FIG. 3. Canine left ventricle 14 days after cryoinjury showing replacement of muscle by granulation tissue at perimeter of the lesion (arrows indicate epicardium) (hematoxylin and eosin, original magnification ×20).

Early microscopic examination of the healing cryolesions revealed hemorrhage and extensive coagulation necrosis with loss of nuclear staining (Fig. 2). Necrosis and granulation tissue persisted in the 14-day specimens (Fig. 3) but was absent in the lesions after 21 and 35 days (Figs. 4–6). Polymorphonuclear leukocytes were present in substantial numbers only in the early lesions. Macrophages, in contrast, were present in the cryolesions harvested between 1 and 3 weeks. Endothelial cell proliferation with new capillary formation (neovascularization) was not evident at 3 days but was markedly present after 7 and 14 days (Figs. 4 and 5). Fibroplasia had started by the 7th day and was most prominent after 14 days (Figs. 3 and 4); this fibroplastic response had started to regress in the 21-day specimens and was absent after 35 days (Figs. 5 and 6). Histologically, collagen deposition was evident in the 7-day specimens and steadily increased thereafter throughout the entire sampling period, as illustrated in Figures 3–6. This pattern was consistent with the quantitative hydroxyproline data [Fig. 1]). No substantial qualitative histologic differences were found between the cryolesions patched with latex rubber and those that were exposed to the pericardium, as summarized in Table 1.

Discussion

The presence of pericardial adhesions surrounding areas of old myocardial infarction has been interpreted to suggest that the pericardium attaches to the myocardium when inflammation is present, perhaps reinforcing the structural integrity of the necrotic tissue or contributing additional blood supply. Historically, surgeons have tried to enhance this process in an attempt to revascularize ischemic myocardium; Beck surgically joined areas of experimental myocardial infarction to the pericardium, greater omentum, and other tissues in hopes of inducing collateral circulation to the heart in 1935.[8] Yamazaki et al. reported fewer arrhythmias, decreased left atrial pressure, and higher left ventricular ejection fractions in dogs after surgical treatment with a synthetic "on lay" patch[9] that covered the infarction and constricted its size by 25%.

The experiments reported herein were designed to demonstrate if more rapid and/or complete healing of a standardized myocardial injury occurred if the pericardium was directly attached to the area of infarction. No difference was seen in the rate at which the patched and the exposed myocardial cryolesions healed. The change in wound depth, furthermore, was uniform over time, with or without the adherent pericardium. No qualitative differences were demonstrated histologically, and no significant quantitative difference in hydroxyproline accumulation was demonstrated between the two groups in this experimental model.

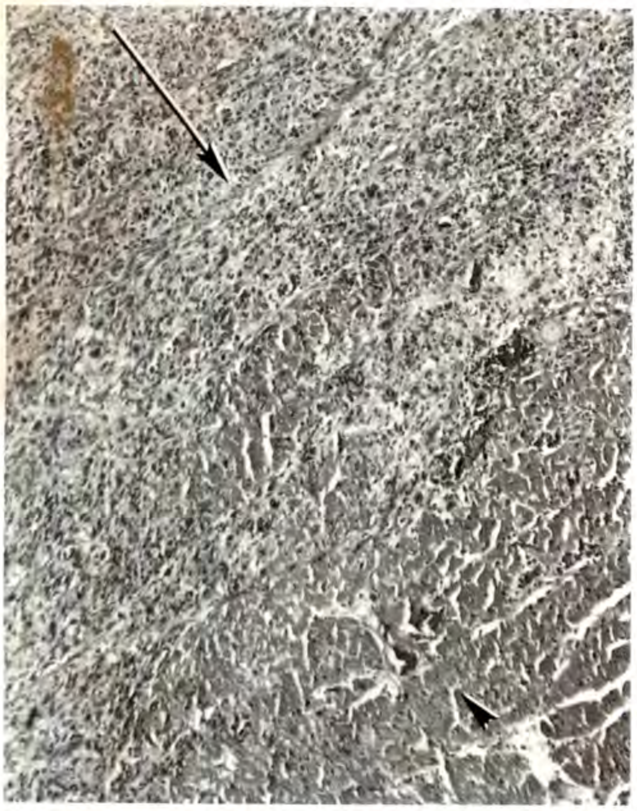

FIG. 4. Left ventricular myocardium from the same heart as shown in Figure 3. Granulation tissue is present (arrow), with viable myocytes below (arrowhead) (hematoxylin and eosin, original magnification ×100).

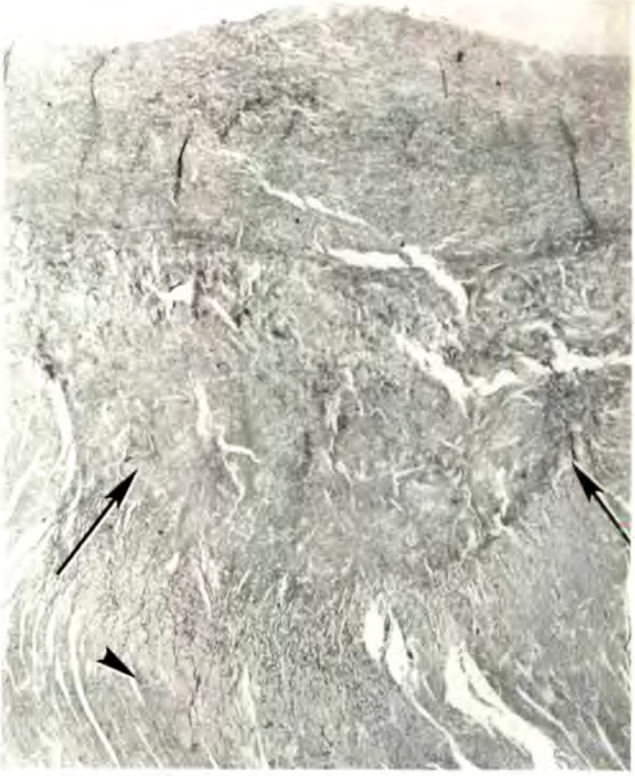

FIG. 5. Canine left ventricle 35 days after cryoinjury, illustrating sharply demarcated scar (arrow). Intact myocardium is present below this scar (arrowhead) (hematoxylin and eosin, original magnification ×15).

We cannot conclude, however, that the pericardium does not protect acutely infarcted human myocardium from ventricular rupture or possibly contributes an element of supplemental blood supply. The lesions in this experiment were not transmural; furthermore, the cryolesions were created in well-perfused and otherwise healthy, uncompromised regions of normal canine myocardium, which has exuberant collateral vascular supply. Therefore, the question as to the role of the pericardium in the healing of human myocardial wounds and infarcts remains unresolved.

These observations did demonstrate that cardiac cryolesions provide a reliable and reproducible experimental model for the investigation of myocardial

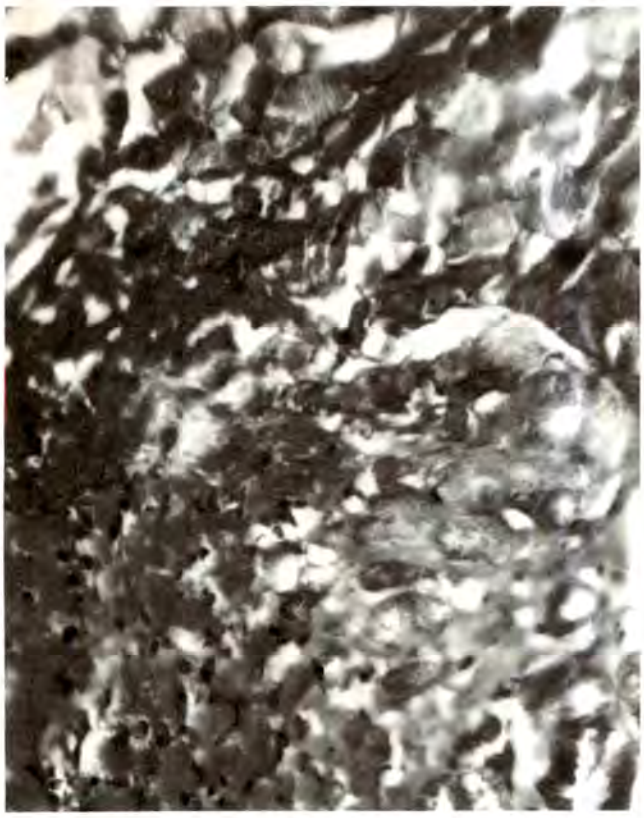

FIG. 6. Same heart as in Figure 5, demonstrating densely collagenous scar with a paucity of cells in the region of the cryolesion (hematoxylin and eosin, original magnification ×200).

wound healing. Unlike the standard technique of coronary ligation, which generates a variable extent and pattern of myocardial necrosis, cryolesions produce a uniform, highly reproducible area of necrosis. The shape of the lesions can be controlled easily by altering the geometry of the cryoprobe. Because the pattern of necrosis extends radially, depth relates to the size of the epicardial lesion. The depth of the injury may also be augmented by increasing the duration of freezing, decreasing the temperature of the probe, and, probably, by applying multiple freezes.[7] It appears that the most reliable way to create transmural lesions is to introduce a trocar cryoprobe through the myocardium.[7]

TABLE 1. *Histologic Observations in the Myocardial Cryolesions at Different Times After Operation**

Histologic Findings	Severity of Histopathologic Changes by Age of Infarct (Days)†					
	3	7	14	21	35	Control
Hemorrhage	3	2	1	0	0	0
Necrosis	3	2	1	0	0	0
Leukocytes	2	1	0	0	0	0
Lymphocytes	0	2	1	0	0	0
Macrophages	0	3	2	1	0	0
Endothelial cells	0	3	3	1	0	0
Fibroblasts	0	1	3	1	0	0
Collagen	0	1	2	3	3	0

* Lesions from both groups were combined in this analysis because there appeared to be no qualitative difference between the two groups.

† Relative severity of histopathologic changes was graded as follows: 0 = absent; 1 = mild; 2 = moderate; or 3 = severe.

Cardiac cryolesions differ from clinical myocardial infarction primarily in the mechanism of injury. Cryogenic injury results in coagulative necrosis, whereas myocardial infarction results from venous hemorrhage after arterial occlusion. Both mechanisms produce necrosis, which heals by interacting with cellular elements of the surrounding myocardium. The histologic studies done in this study reveal that the cellular pattern of healing cryolesions corresponds closely to that seen in healing myocardial infarctions. Granulocytes appear first in the injured area and are later replaced by macrophages. Fibroblasts and endothelial cells migrate to the wound edge; the fibroblasts then produce collagen, within which the endothelial cells form small vessels. This pattern essentially follows that described by Mallory et al.[10] in their classic description of the healing process of myocardial infarction.

One histologic difference between the healing of a myocardial infarction and a cardiac cryolesion was the absence of necrotic tissue after 14 days. Macrophages were not seen in the (cryolesion) wounds after 21 days. This difference probably relates little to the healing process but rather to the size of the original injury or ongoing myocardial ischemia. Because size has not been quantitated precisely in experimental studies of healing myocardial infarction, necrosis and inflamation may persist because of the size and/or shape of the lesion or other factors.

One objection to this model for investigation of myocardial wound healing is the plentiful amount of blood flow in the myocardium surrounding the cryolesion, which may have minimized the potential effect of the pericardium in terms of contributing collateral blood supply. This theoretic problem, however, could be solved by the creation of cryolesions in an area of ischemic (coronary occlusion) myocardium. Coronary artery branches could be ligated distally, where such would not result in a large infarction, thereby possibly reducing the attendant arrhythmias.

An advantage of cryolesions for the investigation of myocardial wound healing is the remarkable consistency of healing; the depth of the lesions decreased and the collagen content of the wounds increased as a function of time. Additionally, the use of cryolesions rather than coronary ligation offers a distinct advantage in terms of early animal attrition. None of the animals died before the date they were to be killed; however, had this method been used to produce larger ares of necrosis or transmural necrosis, the mortality rate might have been greater. This difference probably rests entirely in the relative absence of ventricular arrhythmias.

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Long-term Results with Autogenous Tissue Repair of Traumatic Extremity Vascular Injuries

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With extensive vascular injuries in which a vascular conduit is required, there is controversy as to whether an autogenous or prosthetic graft is preferable. The authors reviewed their experience with 91 extremity arterial injuries in which autogenous tissue was used to repair vascular injuries of the extremities. Twenty-two patients also had concomitant repair of associated venous injuries with autogenous vein grafts. Ten patients required amputations, despite patent grafts in five patients, because of severe muscle necrosis. Two patients had thrombosis of their vein grafts develop in the early postoperative period but did not require amputation. The authors identified only one late vein graft failure in a patient in whom an infected pseudoaneurysm developed. Three patients with extensive soft tissue injuries had infection develop in vein grafts, with subsequent massive bleeding that ultimately required arterial ligation. Among the 22 patients with repair of their venous injuries, occlusion of popliteal vein repairs was documented in two patients and suspected in three others. The remainder of patients had satisfactory results. The excellent results obtained in the vast majority of the authors' patients with extremity vascular injuries reinforces their preference for using autogenous tissue whenever a vascular conduit is required. Exceptions include patients with extensive soft tissue loss precluding adequate graft coverage, the repair of large vessels, and life-threatening emergencies when there is insufficient time to harvest and prepare a vein.

RECENT CLINICAL and experimental studies suggest that prosthetic grafts are satisfactory conduits for the repair of traumatic injuries even in contaminated wounds.[1-11] Our preference has been to avoid the use of prosthetic grafts because of the risk of subsequent graft infection. In addition, prosthetic grafts have inferior patency rates compared with autogenous grafts in elective lower extremity revascularization, which is an important consideration in young patients with long life expectancies.[12] The purpose of this study was to review our results with autogenous veins used in the repair of traumatic vascular injuries with particular reference to late follow-up.

Materials and Methods

We reviewed the records of 91 patients in whom autogenous veins were used to repair extremity arterial injuries at the University of Kentucky Medical Center from 1963 through July 1985. Patients in whom prosthetic grafts were used or in whom primary vascular repair was feasible were excluded. In 22 of these 91 patients, autogenous veins were used to repair associated venous injuries.

Seventy-nine per cent of the patients were male and 21% were female. The mean age was 30.1 years, with a range of 12–74 years. The injuries were caused by blunt trauma in 29% and penetrating trauma in 71%, most of which were secondary to gunshot wounds. There were five deaths, all of which occurred in patients in profound shock on admission from multiple injuries. Thirty-three per cent of the patients had associated bone fractures, 37% had direct nerve injuries, and 19% had extensive soft tissue injuries.

Follow-up data were obtained by chart review, contact with personal physicians, or follow-up examination. Graft patency was determined by physical examination, noninvasive vascular laboratory studies, and, in selected instances, by angiographic or venographic studies. Ten patients were lost to follow-up. The mean length of follow-up among the surviving patients was 33.5 months (range: 1–207 months).

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TABLE 1. *Results of Autogenous Tissue Repair of Traumatic Extremity Vascular Injuries*

Artery (Number of Patients)	Autogenous Graft			Results of Arterial Repair			Causes of Graft Failure			Associated Venous Injuries	Postoperative Amputations
	SV	CV	BV	Excellent	Early Failure	Late Failure	Infection	Technical	Outflow		
Axillo–subclavian (14)	14			13		1				7	
Brachial (28)	23	2	3	24	4		2	1		9	3
Common femoral, superficial femoral, or popliteal (40)	49			43	4		1	1	2	29	6

SV = saphenous vein; CV = cephalic vein; BV = basilic vein.

Results

The location of the arterial injuries, types of autogenous grafts used, and results are listed in Table 1.

Axillo–Subclavian Arterial Injuries

Among the seven patients with associated venous injuries, four veins were repaired with interposition saphenous vein grafts and one with a saphenous vein patch. The subclavian vein was ligated in two patients with no subsequent edema. All venous repairs appeared to be patent.

Among the 14 arterial repairs, the single late vein graft failure was the development of an infected pseudoaneurysm (*Staphylococcus aureus*) 8 months after operation, which was treated by ligation. The patient has a viable upper extremity. Several patients continue to have significant functional impairment from their associated neurologic injuries.

Brachial Artery Injuries

Of the four early graft failures, one graft thrombosed because of compression from a muscle flap that was rotated to cover a large soft tissue defect. Another graft thrombosed because of extensive distal thrombosis. There had been a several-hour delay between injury and subsequent revascularization in this patient. Both patients have mildly ischemic extremities but did not require amputation.

In the two patients whose autogenous vein grafts became infected, there was massive soft tissue loss that had precluded adequate soft tissue coverage of the grafts. The wounds subsequently became infected with multiple organisms, and both grafts bled massively several days after operation. At re-exploration, the bleeding sites were in the mid-portions of the vein grafts, and it appeared that a portion of the vein wall had become necrotic. A second saphenous vein graft was placed in one patient, but it subsequently became infected, with recurrent massive hemorrhage. Both patients ultimately required ligation of the brachial artery, which resulted in mildly ischemic extremities.

The venous injuries were ligated in all patients, and none of the patients had edema develop. Three patients required amputations early after operation because of extensive muscle necrosis. All three patients had severely ischemic extremities on admission because of a long delay between injury and restoration of circulation.

Common Femoral, Superficial Femoral, or Popliteal Artery Injuries

Among the 29 patients with concomitant venous injuries, interposition saphenous vein grafts were used in 14 patients and saphenous vein patch grafts were used in two. The venous injuries were repaired primarily in 11 patients. The popliteal vein was ligated in two patients, both of whom required amputation.

Six amputations were required in the early postoperative period because of extensive muscle necrosis, despite patent grafts in two patients. Once again, there had been a long delay between injury and revascularization in these two patients.

There were four early graft failures, all of which resulted in amputation. Technical error appeared to be the cause of graft failure in one patient. Venous outflow occlusion was the likely cause of graft failure in another patient in whom the popliteal vein was ligated when exploration was performed initially at another institution, and it was not possible to restore patency of the popliteal vein. In addition, the saphenous vein that was used for the interposition graft was harvested from the injured extremity, which likely increased his venous hypertension. Another graft failure occurred in an elderly patient in whom all three tibial arteries were severely atherosclerotic. The long delay between injury and revascularization in this patient resulted in extensive distal thrombosis.

The fourth graft failure occurred in a patient with a large soft tissue defect precluding adequate coverage of the graft. The wound became infected with multiple gram-positive and gram-negative organisms, with subsequent profuse bleeding from the vein graft. Another saphenous vein graft was placed, but recurrent hemorrhage developed and a third interposition vein graft was placed. Several weeks later, a large infected pseudoaneurysm developed, and the patient required an above-knee amputation. Pathologic examination of the vein graft demonstrated aneurysmal dilatation and necrosis in the vein wall.

Among the 14 interposition vein grafts used to repair associated venous injuries, there were two failures documented by venographic studies. Three patients require support stockings to control mild edema, but no venographic studies were done to determine patency of the venous repairs.

Discussion

In treating traumatic vascular injuries, primary repair of the damaged vessels is the preferred method of treatment. However, extensive damage to the vessels precludes primary repair and necessitates either ligation of the vessel or use of a vascular conduit. Because ligation of critical arteries such as the popliteal artery results in a prohibitively high amputation rate, surgeons have been aggressive in attempting to repair major vascular injuries.

When primary vascular repair is not feasible, there are three options. The first is to use autogenous tissue, most commonly saphenous vein. The second option is to employ prosthetic material, usually Dacron or polytetrafluoroethylene (PTFE). Prosthetic grafts are often required in the repair of major intrathoracic or intra-abdominal arteries because of their large size. A third option is to perform an extra-anatomic bypass with either a prosthetic or autogenous graft, thus avoiding a potentially contaminated area. The advantages of this approach in the treatment of popliteal artery injuries were outlined in a previous report from this institution.[13]

There are conflicting results reported with prosthetic grafts used to repair traumatic vascular injuries. In their report on the military experience in Vietnam, Rich and Hughes noted a prohibitively high incidence of prosthetic graft failure among patients with traumatic vascular injuries who had contaminated wounds.[14] Infection and thrombosis were the most common causes of graft failure. Massive life-threatening hemorrhage often accompanied the infection. In distinct contrast to these poor results, there are a number of reports from major civilian trauma centers describing very satisfactory results with prosthetic grafts, usually PTFE, used to repair vascular injuries both in the arterial and venous systems.[2-5,11] However, one series reported a 29% late occlusion rate among PTFE grafts used to repair arterial injuries and a 100% occlusion rate among the PTFE grafts used for the repair of venous injuries.[11] Certainly such a high occlusion rate argues the routine use of prosthetic grafts in vascular trauma, particularly when the vast majority of patients are young.

One would intuitively expect a high incidence of infection among prosthetic grafts that are placed in contaminated wounds. However, several clinical and experimental studies suggest that prosthetic grafts may be superior to autogenous tissue grafts in contaminated wounds.[1-10] In one series of patients with traumatic vascular injuries for which interposition grafts were required, 12 perigraft infections developed, five of which occurred in patients with Dacron grafts, and seven patients had infection develop in saphenous vein grafts. In five of the seven vein graft infections, the vein graft subsequently disrupted with profuse hemorrhage in all five patients. In contrast, among the patients with infected Dacron grafts, three patients had intermittent anastomotic bleeding with pseudoaneurysm formation, but there were no episodes of gross hemorrhage. Among those with infected Dacron prostheses, there were "sentinel" bleeding episodes that heralded the anastomotic breakdown, but there were no episodes of profuse hemorrhage. Because these "sentinel" bleeding episodes allowed time for corrective measures such as graft removal or extra-anatomic bypass, the authors felt that Dacron was preferable to autogenous vein in potentially contaminated vascular injuries when extra-anatomic bypass with autogenous tissue was not feasible. In addition, there are a number of antecdotal reports of patients exsanguinating as a result of dissolution of an infected saphenous graft that had been used to repair traumatic vascular injuries.[7,15-17] A common factor in all of the patients with infected vein grafts and massive bleeding has been a massive soft tissue defect and a contaminated wound.

Experimentally, prosthetic grafts appear to tolerate infection better than autogenous grafts.[6-10] In a study comparing infected PTFE and vein grafts in canine femoral arteries, transmural necrosis with exsanguinating hemorrhage occurred in six or seven infected vein grafts where only two of seven infected PTFE grafts bled.[9] The bleeding in the two animals with infected PTFE grafts resulted from necrosis of the host artery at the anastomotic site. Other experimental studies have confirmed the tendency of autogenous vein grafts to undergo transmural necrosis when infected.[6,8,10] In contrast, the bleeding seen with infected prostheses results from host artery necrosis at the anastomosis, and exsanguinating hemorrhage is rare.

Once a vein graft becomes infected and bleeds, the native artery should be ligated proximal and distal to the point of infection. In two of our three patients with infected vein grafts that bled, multiple attempts at revascularization with fresh saphenous vein grafts were made, but profuse, recurrent hemorrhage occurred in both. Similar disastrous results with multiple attempts at revascularization in the presence of gross infection were reported by Rich et al. from Vietnam, and we completely agree with their opinion that multiple attempts at revascularization in the presence of infection are ill-advised.

The critical factor that seems to predispose autogenous or prosthetic grafts to infection appears to be a lack of adequate soft tissue coverage.[2,11,15–17] In our study, all three patients with infected vein grafts had massive soft tissue loss. It has been postulated that bacterial infection prevents contact between the vein graft and host tissues by its inflammatory action and also introduces an element of collagenase activity that can lead to transmural necrosis and disruption of vein grafts.[2]

In an effort to provide coverage of exposed vein grafts, Ledgerwood and Lucas used porcine grafts as temporary biologic dressings with good results.[18] Major soft tissue reconstruction has been attempted at the time of the initial vascular repair, but the results have been disappointing.[17]

When there is massive soft tissue loss precluding adequate soft tissue coverage, or if there is gross contamination of the wound, we believe that there is a definite role for prosthetic grafts if an extra-anatomic bypass with an autogenous or prosthetic graft through undamaged tissue planes cannot be performed. Our preference would be to use a PTFE graft as a temporizing measure until wound sepsis has been controlled and the wound is ready for major soft tissue reconstruction. At the time of definitive soft tissue reconstruction, consideration should be given to replacing the prosthetic graft with an autogenous vein graft because of the superior patency rates with autogenous vein grafts in lower extremity revascularization.[23]

The patency rates with autogenous vein grafts in our study were excellent, because we identified no late graft occlusions. Because several of our patients were lost to long-term follow-up and follow-up arteriograms were performed on only a few patients, it is certainly possible that our incidence of late graft failure might have been considerably higher had we been able to obtain long-term follow-up information on all patients. Graft occlusion could have occurred in some of these patients, with the patients remaining asymptomatic because of excellent collateral circulation. In the Vietnam military experience, Rich et al. noted that 24 of 34 patients with thrombosed arterial repairs did not require operative intervention, attesting to both the ability of collateral circulation to provide adequate circulation as well as to the fact that these patients are often limited in their activities by their associated neurologic deficits.[22] However, we believe that our low incidence of graft infection is accurate because these patients would have undoubtedly returned to this institution for treatment of any graft infection.

Our satisfactory long-term results with autogenous tissue have encouraged us to advocate its use in the vast majority of traumatic vascular injuries in which primary repair is not feasible. However, there are situations in which the use of prosthetic grafts is preferable, if not mandatory, such as in the repair of large intrathoracic or intra-abdominal arteries, when the large size of the vessels necessitates the use of a prosthetic graft. Patients with multiple associated injuries or those who are hemodynamically unstable may also be better served with a prosthetic graft rather than by additional time being taken to harvest a vein graft. Should subsequent reconstruction be required in these patients because of thrombosis or infection of the prosthetic graft, elective revascularization with autogenous vein grafts can be performed.

In patients with large soft tissue defects and potentially contaminated wounds, we believe that an extra-anatomic bypass with either an autogenous or prosthetic graft through noninfected tissue planes should be considered. When this is not feasible, consideration should be given to use of a prosthetic graft such as PTFE because it appears to tolerate subsequent infection better than autogenous tissue and the reported short-term patency rates are satisfactory.

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Editorial

A Future for Surgical Critical Care?

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CRITICAL CARE MEDICINE is an exciting new medical specialty to some and a bad dream to others. Attempts by the Society of Critical Care Medicine to mold a consortium of specialties into one have been unsuccessful, but, despite this failure, the need for appropriate critical care has not disappeared.[1] The surgical intensive care unit is vital to surgical patients requiring supportive care before and after an ever-widening range of complex procedures. How will surgeons meet the needs of their patients in the intensive care unit? In particular, can academic surgical centers establish surgical critical care as a medical specialty in an educational environment?

Surgical patients are placed in a surgical intensive care unit for many reasons, but, in broad terms, their needs are reduced to organ monitoring, fluid resuscitation, and cardiopulmonary support. Providing immediate care for these patients is often difficult because surgeons are required to spend more time in the operating room performing increasingly difficult, intricate, and time-consuming procedures. One answer to this scenario is to relinquish care of the surgical patient to an intensivist.[2] This option is not acceptable to a surgical education program and is questionably appropriate for excellent surgical care. The converse solution is to have each surgeon care for his or her patients. Unfortunately, time commitments, training, and experience of all surgeons do not make this an attractive solution either. A final choice is to manage these patients with a medical committee, which has already been criticized as self-serving, inefficient, and costly. This dilemma in surgical care will not go away, and we must find a solution within our resources.

The American Board of Surgery is attempting to resolve this problem by establishing a specialty certificate based on training and experience requirements. This is a beginning but cannot be considered an answer. This beginning implies that surgical intensive care should be provided to surgical patients by surgeons. The advantages of surgical involvement include the following: (1) surgical diseases are already known by the critical care consultant; (2) basic surgical principles are similar among operating and critical care surgeons; (3) educational programs can be developed for better surgical education within the basic residency and surgical critical care programs; and (4) surgical patients benefit from a knowledgeable and available provider of critical care.

However, where are these surgeons? At the present only a handful of surgeons practice critical care. This is not surprising because the club is usually entered by doing a critical care fellowship that is commonly designed without operative experience and surgical mentors. This approach is hardly a way to attract young surgeons to a discipline and a poor way to instill faith in a trainee's capability with other surgeons. Our credibility must be established among surgical peers, so that we are viewed as operative surgeons who are active in surgical critical care.[3]

The major disadvantage of having surgeons provide critical care is its similarity to our first option of using

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intensivists, to whom the operative surgeon relinquishes his or her patient's care. Although it is similar, it is not the same. Surgeons speaking to surgeons have a better chance of communicating about their patients' problems because of their common backgrounds. Furthermore, the operative surgeon must remain the patient's primary physician and have the final say regarding patient care. The organizational plan is a cooperative team effort with one captain, the operative surgeon. The team players have mutual respect and confidence for one another as they achieve their goal of excellence in surgical critical care. Furthermore, educational programs will benefit because surgical trainees will become familiar with all types of surgical patients requiring critical care.

Can this solution be applied in nonacademic environments? It certainly is possible, but variations of this organizational scheme will be more realistic and will possibly include nonsurgeons as providers of surgical critical care. However, the design of these variations will most certainly be helped if surgical trainees have an organized and favorable experience in surgical critical care provided by their surgical professors.[4]

Unless we begin to develop surgical critical care, the surgeon's role will predictably decrease, despite our vociferous good intentions. Our efforts must be united to avoid internal disputes among specialties fighting for their turf in the surgical intensive care unit.[5] Already an attitude exists that critical care is different among surgical specialties and competency should be controlled by each surgical specialty. This is truly fragmentation of surgery at its best, or worst, and can only serve to guide surgical critical care down a narrow and winding path leading to mediocrity and self-destruction.

Critical care must be embraced as a branch of the tree of surgical knowledge that is practiced by fellow surgeons with an appropriate fund of information. These efforts must be supported by all surgeons and surgical disciplines so that the expertise in perioperative care the surgical critical care specialists possess complements our operative expertise while primary surgeon–patient relationships are respected. This is a tall order but one that can be accomplished if a cooperative approach to surgical critical care is accepted by all surgical disciplines. We must acknowledge surgical critical care as a necessary surgical discipline and establish guidelines to teach surgical critical care within our training programs. Without this recognition, cooperation, and planning it is likely this branch will never bear fruit.

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Editorial Review on "A Future for Surgical Critical Care?"

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THE ARTICLE by John A. Weigelt, M.D., "A Future for Surgical Critical Care?", usefully highlights some of the problems and the promise of the Certificate of Added Qualifications in Critical Care. Dr. Weigelt addresses several points of concern now that surgical critical care has evolved into an area of special interest recognized by the American Board of Surgery through a Certificate of Added Qualifications.

Weigelt correctly dismisses as improper the prac- of surgeons relinquishing the postoperative care of their patients to nonsurgeons, even though it is the *modus operandi* in many academic and community medical centers. However, he is concerned about the paucity of surgeons who could properly be called "intensivists." He notes that credibility in critical care by surgeons must be established among surgical and medical peers. A "surgical intensivist" must also be respected as an operative surgeon. A surgeon who has administrative and clinical capabilities in intensive care must have competence equivalent to critical care peers in other disciplines, for example, anesthesiology, internal medicine, and others.

The evolution of intensive care as a specialty has a complex history. Although recovery rooms have become prevalent only in the last 25 years, in 1863 Florence Nightingale observed "it is not uncommon in small country hospitals to have a recess or a small room leading from the operating theater in which the patients remain until they have recovered or at least recovered from the immediate effects of the operation."[1]

In 1923 W. E. Dandy developed the concept at Johns Hopkins of a neurosurgical intensive care unit (ICU). A combined recovery room and ICU was common in some German universities as early as the 1930s. In North America, the first coronary care units were established in 1962. The evolution of cardiac surgery has led to the further development of this concept and further specialization.[2]

In Scandinavia, the mortality rate from respiratory paralysis associated with polio was high in the 1940s. The development of many ventilators evolved because of polio epidemics. The development of dialysis and burn units, as well as other labor-intensive patient care organizations, has logically resulted in people having special expertise.[3-6]

Equally important to skill in intensive care is availability of facilities and number of staff members. Other issues such as cost containment, administrative expertise, and others must be considered in the management of the modern ICU, and, to this end, a National Institute of Health consensus group recently developed standards for ICUs and recommended four category levels based primarily on nurse:patient ratios.[7-10]

Complex professional concerns relating to specialization and fragmentation are part of the debate regarding further specialty designations. Although specialization is a legitimate and useful application of knowledge benefitting patients with special needs, fragmentation frequently must bear the onus of being self-serving. In contrast to both, the concept of additional credentials is more consistent with the background of specialties such as internal medicine, pediatrics, and anesthesia with shorter core training programs than surgery. Nevertheless, today almost 60% of the people finishing residency education in general surgery, which has a 5-year minimal requirement for Board eligibility, opt for additional education. This tends to produce a core of people who wish formal recognition, be it in cardiothoracic surgery, colon and rectal surgery, plastic surgery, surgical critical care, or other specialties. Unfortunately, Added Qualifications are interpreted as essential for issuing credentials by many hospital boards. It is not uncommon for the

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American Board of Surgery to receive inquiries requesting verification of a Diplomate's education in a special area such as vascular surgery, such inquiry being directed toward making a ruling about privileges in that area and probably requiring the additional certification for these privileges.

As pointed out by Walt, "the central question for surgeons is whether the patient in the surgical intensive care unit is better served by a surgeon or a non-surgeon as the responsible physician and the administrator of the SICU."[1] Unfortunately, available data describing the surgeon's role in the ICU are not extensive. Machiedo (1980) surveyed academic surgical departments in the United States and found the following: (1) 61% had surgeons as surgical intensive care unit (SICU) directors, and 93% were pleased with that arrangement; (2) 84% felt that involvement in the ICU did not detract from a surgeon's central role as an operator; (3) paradoxically, rotations of surgical residents through the ICU were available in only 55% of the programs and usually for only 1 or 2 months while they were junior residents; (4) Fellowships in Critical Care were minimally available; (5) Canadian surgeons, who may have more experience with ICUs than American surgeons, have become comfortable, as have surgeons in the United Kingdom, with anesthesiologists dominating the ICU scene; and (6) most people surveyed felt that Fellowships should, and could, be incorporated into a 5-year surgical residency, and only a minority favored the establishment of a special certificate.[8]

In 1983 the Pre- and Postoperative Care Committee of the American College of Surgeons conducted a broader survey and found out that SICUs were under the direction of surgeons in only 39–61% of the institutions polled. The lower representation was found in not-for-profit private hospitals. This survey suggested that surgeons were delegating the care of patients in the ICU to others, perhaps to other specialists. The survey resulted in additional conclusions: (1) 54% of the respondents agreed that "surgeons are abandoning ICU patients to non-surgical specialists"; and (2) in 50% of the SICUs, residents other than surgery residents might write orders.[14]

The Society for Critical Care Medicine, which includes a surgical section, has continued to be interested in a special certificate.[12,13] A Joint Committee for Critical Care Medicine, composed of representatives from the American Boards of Anesthesiology, Internal Medicine, Pediatrics, and Surgery, was first formed in 1979 to address the issue of additional certification in critical care. The Committee's deliberations over several years identified preliminary requirements and a method of application and even produced a number of questions to be used on a written examination. However, in 1983 the American Board of Internal Medicine withdrew from the joint committee, followed shortly by the withdrawal of the American Board of Pediatrics. The committee collapsed. The individual Boards then considered applying to the American Board of Medical Specialties separately for permission to award an additional certificate in critical care.

At the American Board of Surgery, the discussions were pointed and often heated and revolved around two opinions: (1) critical care and general surgery are synonymous and therefore no critical care certificate was needed; and (2) if other Boards were going to award a critical care certificate, the Diplomates of the American Board of Surgery should have access to a similar certificate. The latter opinion received the majority vote at the June 1984 meeting. In 1985, the four previously mentioned specialty Boards were granted permission to award a Certificate of Special Qualifications in Critical Care. This was subsequently changed by the American Board of Surgery to a Certificate of Added Qualifications in Surgical Critical Care. It is important to note that in all four proposals regarding critical care certification, the American Board of Medical Specialties insisted on a statement that the person who is the patient's primary physician must remain so, regardless of who is caring for certain features of the patient's care or where the care is rendered.

There are multiple objectives associated with the decision by the American Board of Surgery to award a Certificate of Added Qualifications in Surgical Critical Care. One is to assure the level of preparation of the surgeon in order to continue to care for the "sick patient." Moreover, we must maintain our ability to care for our patients in all locations, with the same capabilities that will be available from other specialists. One beneficial feature of the decision to offer a Certificate of Added Qualifications in Critical Care will be the renewed involvement of surgeons in critical care as an educational process.

The Residency Review Committee for Surgery has focused attention on education in critical care. With the rapid growth of group practice, more cross-coverage and team care is occurring in the practice of surgery. Many group practices have people within the group who bring different special contributions to a practice. Expertise in critical care is an appropriate additional dimension. Research in the arena of critical care has long been a focus of activities of surgical investigators. Our understanding of shock, resuscitation, infection, nutrition, fluid and electrolytes, immunology, and other areas are greatly enhanced and stimulated by the "living laboratory" of the ICU.

Again, citing Walt, "The task of caring for the critically ill is not one for the amateur, for the unavailable, for the narrow-minded, and probably not for the imperious or ignorant. To the extent that we do not fit these categories, we are assured of our place in the surgical intensive care unit unless we resign it by default. If we were to be displaced from the surgical intensive care unit by cognitive gurus, this would feed and confirm the prejudice of those who wish to promote the picture of the surgeon as a technician."[1]

In this day of the "arms race" of Added Qualifications and Special Certificates, the best approach to the issue of critical care certification is to work toward enhanced education in the ICU setting for general surgery residents. However, a segment of our surgical residents should be encouraged to follow a pathway beyond first certification leading to Added Qualifications in Surgical Critical Care. To do less would be to abandon an essential feature of the care of patients with life-threatening illness.[15]

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Book Reviews

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Cardiac Surgery, 2nd Edition, in the series **Cardiovascular Clinics.** Dwight C. McGoon. 446 pp. Philadelphia: F. A. Davis Co. 1987. $75.00.

THIS BOOK admirably reflects the unique credentials and qualifications of the editor. The 22 chapters arranged in six sections are written by surgeons who, like Dwight McGoon, have immense practical experience, a scholarly appreciation of cardiac surgical science, and a capability for clear and concise exposition. The result is a volume of genuine merit that provides a highly readable synopsis of current cardiac surgical capability across the entire breadth of the discipline.

The prologue and epilogue by Dr. McGoon provide parameters of historic evolution and visions of the future from his perspective as a practitioner, innovator, author, and editor. The section on coronary heart disease contains eight chapters. Remaining sections are dedicated to valvular disease, congenital heart disease, aortic diseases, operative and postoperative developments, and emerging advances consisting of two to four chapters each.

There is some variation in style between chapters but none in quality. Reference lists with each chapter are well selected and remarkably complete without being tediously long. Illustrations are of excellent quality and sufficiently numerous to adequately elucidate many recent advances in technique, although the book is not designed to be an atlas.

The particular strength of this book is the achievement of a concise summary of a broad range of topics covering the entire field of cardiac surgery without being either incomplete or superficial. With 423 pages it is of manageable size for a briefcase.

This book is ideal for the practicing cardiologist or cardiology fellow wishing to grasp the essence of modern cardiac surgery. For experienced cardiac surgeons it will provide a painless review because the authors took the time to be brief. For cardiac surgical residents, registrars, and fellows it represents a rare opportunity to gain a knowledge of practice and perspective in the most rapidly progressing surgical specialty, which has yet emerged in medical practice.

JOHN J. COLLINS, JR., M.D.
Boston, Massachusetts

Surgical Treatment of Congenital Heart Disease, 3rd Edition. Grady L. Hallman, Denton A. Cooley, Howard P. Gutgesell. 235 pp. Philadelphia: Lea & Febiger. 1987. $45.00.

THIS POPULAR TEXT by Drs. Denton A. Cooley and Grady L. Hallman (1st Edition, 1966) has been revised and published as a 3rd Edition. This new volume includes a third author, Dr. Howard P. Gutgesell, a pediatric cardiologist who has substantially expanded the sections on diagnosis, in particular echocardiography and cardiac catheterization. Another important addition is the excellent chapter on the surgical treatment of cardiac dysrhythmias. Throughout the book, the reproductions of the x-rays, cine angiograms, and echocardiograms are of the highest quality; the drawings of the various surgical techniques are lucid and focus on the most important steps of the operations.

Although the authors in the preface to the latest edition recognize the trend towards early primary intracardiac correction of congenital cardiac defects in the very young, including the neonate, the text reflects, however, a more conservative attitude. Two-stage approach, *i.e.,* palliative operation early in life followed by a later repair, is advocated for a number of defects causing critical disease in infancy, such as tetralogy of Fallot, transposition of the great arteries (with or without VSD), truncus arteriosus, and others. Repair of transposition of the great arteries by Mustard operation, for example, is recommended at 12 months of age after initial palliation with either a balloon atrial septostomy or, if necessary, by blade septostomy in contrast to the current trend to repair in infancy, preferably by arterial switch.

Certainly, for a few remaining lesions such as single ventricle, hypoplastic left heart syndrome, with or without aortic atresia, pulmonary atresia with intact ventricular septum, and tricuspid atresia, a two-stage approach remains the only option at this time. Unfortunately, these challenging surgical problems were either not included at all in this text or were dealt with in a very abbreviated fashion under the common rubric of miscellaneous anomalies.

Another important trend in the management of congenital heart disease to which the authors do not allude, is the treatment in many centers of some of the simple lesions, *i.e.,* patent ductus arteriosus, pulmonary and aortic valve stenosis, by enterprising pediatric cardiologists rather than surgeons. Invasive catheterization techniques, such as balloon catheter dilation of stenotic aortic and pulmonary valves and also of stenosis of pulmonary or systemic arteries have proven very effective. Our pediatric cardiology colleagues are also very successful in manipulating umbrella-like devices to obliterate patent ducti (except in the premature neonate) and in implanting various types of coils to occlude aortopulmonary collaterals or other residual (including surgical) shunts.

Dr. Cooley and his associates have accumulated a very large experience with cardiac transplantation. It is therefore surprising and regretable that the authors did not include a chapter on heart and heart-lung transplantation in the pediatric age group.

Finally, it would have been useful for the reader to be offered a breakdown of the operative and late mortality statistics. Obviously, the overall results reflect the pioneering effort of this world-renowned institution in the development of surgery for congenital heart disease. Consequently, a higher operative mortality is to be expected. However, much has improved over the ensuing years, including the early and late surgical mortality for most congenital heart defects. By presenting the global mortality, the reader cannot appreciate the historic evolution of improved surgical results nor can one gain insight into present day expectations and standards of care.

According to this distinguished group of authors, *Surgical Treatment of Congenital Heart Disease* was not meant to offer an exhaustive review of every aspect of congenital heart disease, but was meant to describe the techniques that are in daily use for the management of the more common lesions treated at the Texas Heart Institute. Within this context, this superbly illustrated and well-documented atlas fulfills its goal.

ALDO R. CASTANEDA, M.D.
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The Soft Tissue Sarcomas. Frederick R. Eilber, Donald L. Morton, Vernon K. Sondak, James S. Economou. 316 pp. Orlando: Grune & Stratton, Inc. 1987. $69.50.

THIS TOME of 22 chapters represents a comprehensive treatise of soft tissue sarcomas edited by recognized oncologic authorities from UCLA. The editors have organized the first comprehensive volume that addresses the clinicopathologic features and management for soft tissue sarcomas of various organ sites.

The Soft Tissue Sarcomas provides a descriptive, highly readable, well-organized approach to the epidemiology, staging, and clinical considerations for management of these rare neoplasms. These highly complex lesions are classified with pathologic descriptions offered for the various tissue types. Authors address the considerations of history (*e.g.*, site, size, growth rates, etc.) as an important overall assessment of disease. Approaches to obtain appropriate pathologic tissues with needle-biopsy/aspiration cytology techniques *versus* open biopsy are described with regard to operative planning. All photomicrographs are black and white but provide adequate depiction of salient histology. A section reviews staining characteristics, immunopathology, and electron microscopy that differentiate sarcoma variants and correlates these parameters with light microscopy. A summary of the clinicopathologic features of the principle soft tissue sarcomas represents a major feature of the text and should be of considerable value to the pathologist and the surgeon.

A chapter devoted to radiologic diagnostic modalities for sarcomas includes: conventional radiography of the chest, tomography, xeroradiography, and ultrasonography. Representative illustrations of these modalities are excellent and enhance the text. Separate sections consider computed tomography, magnetic resonance imaging, angiography, and lymphangiography. Although brief and descriptive, these state-of-the-art modalities enhance the diagnostic capability to allow operative planning and place in perspective the role of comprehensive evaluation *before* surgical intervention.

The authors consider conventional and investigational chemotherapy for these tumors and the results for available single agents. Chemotherapy protocols recommended for the management of low-grade spindle, high-grade spindle cell, small cell, and pleomorphic sarcomas are reviewed. Additionally, a section comprehensively discusses radiation therapy and radiobiology for the various cell types. Authors develop the concept of dose-response curves and the effectiveness of radiation to control subclinical disease. The overall advantages of radiation therapy alone *versus* its combination with surgery is objectively reviewed in the preoperative and postoperative setting. This section briefly enumerates response rates of chemotherapy given as an adjuvant before operation.

The student of this disease will appreciate the comprehensive discussion of sarcomas for various anatomic sites (nervous system, head and neck, lung, chest wall and trunk, breast, cardiac, gastrointestinal tract, hepatobiliary, genitourinary, gynecologic, retroperitoneum, and extremities). Review of each of these organ-specific sarcomas includes the diverse clinical presentations, diagnosis, staging, and clinical management. Most sections are thorough and well supported with illustrations and a comprehensive bibliography. Authoritative approaches for the therapy of pulmonary metastases and the management of pediatric sarcomas are included. Such difficult challenges are considered in a concise, articulate, and scholarly manner. Potential application of immunotherapy is presented from a historic and therapeutic standpoint.

Overall the text is carefully organized and structured to provide the clinician and pathologist involved with the care of soft part sarcomas a well-referenced, contemporary approach to the diagnosis and management of this neoplasm. It is recommended to the surgeon as the definitive textbook on soft tissue sarcomas.

KIRBY I. BLAND, M.D.
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Manual of Critical Care. Frank B. Cerra. 802 pp. St. Louis: C. V. Mosby Co. 1987. $24.95.

THIS BOOK'S preface states that the care of the critically ill patient has produced a multidisciplinary fund of knowledge and experience. A stated goal of the book is to begin the dissemination of this common knowledge to the student, resident, fellow in training, and surgical practitioner. This goal is achieved.

The book is divided into four parts: (1) general principles of physiology and metabolism of ICU patients; (2) organ dysfunction; (3) systemic dysfunction; and (4) therapeutics. An outline style is used, although some chapters are more completely outlined than others. The metabolic, arrhythmia, cardiac pacing, renal dysfunction, and hepatic dysfunction chapters are examples of complete outlines. The remaining chapters are good, although the pulmonary dysfunction and central nervous system chapters are not as detailed as the rest. The outline form is easy to read and should allow the book to be used as a quick reference. In some areas, further reading will be necessary, but the text does give an adequate reference list at the end of each chapter.

The content is generally excellent. Many diverse facts and figures are now obtainable in this simple compact text. When appropriate, such as in the airway chapter, the reader is instructed in the basic principles of how, what, why, and where. At other times the content is dedicated to difficult problems with diagnosis or therapy such as in the discussion of different modes of ventilation and weaning the difficult patient. The multiple charts outlining common problems, their causes, and ideas for correction is another strong area.

Some therapeutic content might be questioned as local habit of the individual authors. Problem areas include the discussion of pneumatic antishock garments, use of platelets, and use of fresh frozen plasma. However, these criticisms are small compared to the vast areas of knowledge the book covers.

I believe this book will be invaluable to the surgical trainee involved with critically ill patients and it will give the surgical practitioner a glimpse of a rapidly developing new field in surgery. I believe it will be a valuable addition to your practical surgical library.

JOHN A. WEIGELT, M.D.
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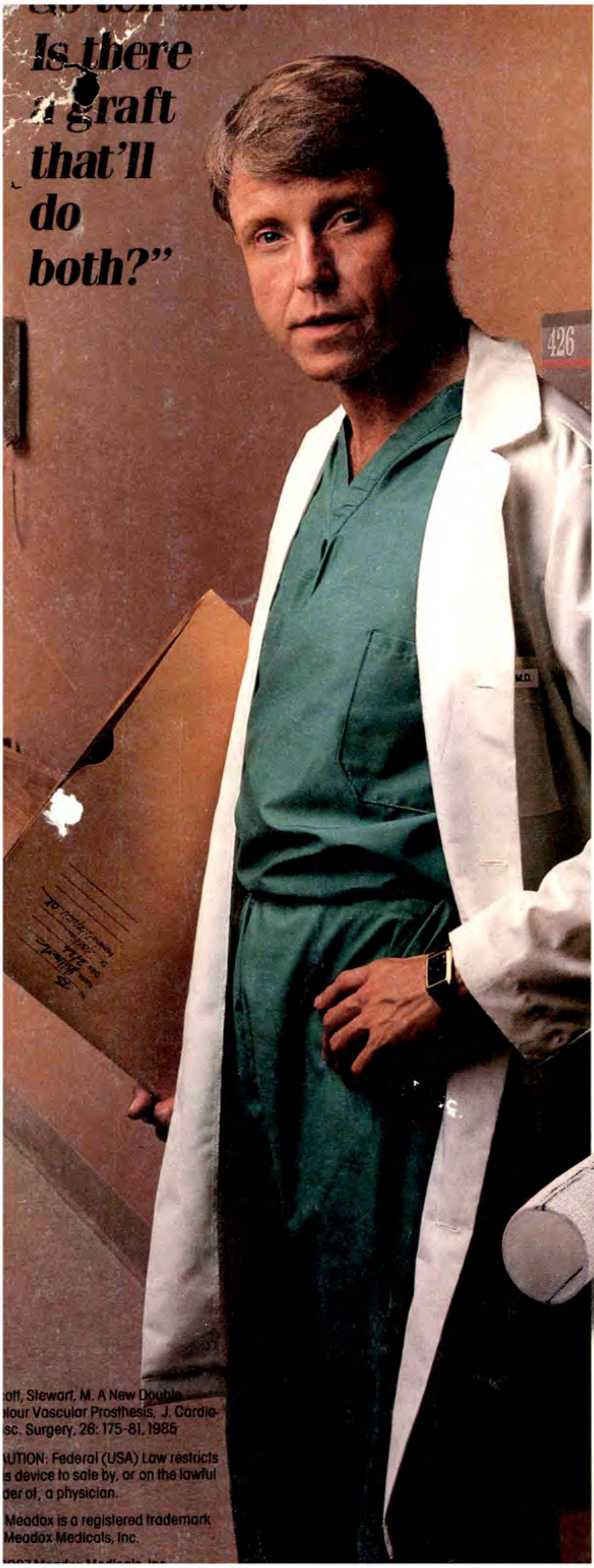

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